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OBSERVATIONS ON THE EFFECTS OF ANTI-HISTAMINE DRUGS ON THE REACTIONS OF THE SKIN VESSELS TO CARBAMINOYL CHOLINE.

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The part played by cholinergic mechanisms in skin pathology has received relatively little attention. In 1936, however, Grant, Pearson, and Comeau concluded from a study of a series of cases of urticaria of nervous origin that this condition is produced by the release of acetylcholine in the skin as a result of stimulation of cholinergic nerve fibres. Their findings have subsequently been corroborated and extended (Hopkins, Kesten and Hazel, 1938 ; Nomland, 1944 ; Loewenthal, 1949).

Experimental evidence of a more indirect nature, which suggests that acetylcholine may be involved in the pathogenesis of certain types of vesication, is provided by the demonstration (Thompson, 1946) that contamination of rat skin with mustard gas or other related vesicants is associated with an inhibition of the specific cholinesterase present in skin (Thompson and Whittaker, 1944). Alexander, Elliott and Kirchner (1940) had earlier claimed that eserine is a powerful urticariogenic substance when introduced into the skin by iontophoresis.

The appearance and behaviour of the skin reactions both to eserine and to carbaminoyl choline, introduced iontophoretically, closely resemble the histamine-induced triple response, and Grant, Pearson and Comeau (1936) have suggested that the intradermal release of acetylcholine in patients with neurogenic urticaria may, in turn, lead to the liberation of H-substance from the skin cells. To obtain further information on the nature of the response of the skin vessels to cholinergic substances, a comparison has been made of the effects produced by certain anti-histamine drugs on the reactions of the skin vessels both to histamine and to carbaminoyl choline.

Method.

Eighteen healthy volunteers of both sexes, between the ages of 20 and 40, were the subjects of the investigation. The test substances were aqueous solutions of carbaminoyl choline chloride (B.D.H.) 1 : 100 and histamine hydrochloride (B.D.H.) 1 : 100,000 and 1 : 1,000,000. Carbaminoyl choline ("Carbachol") was chosen instead of acetylcholine, because of its greater stability when introduced into the skin. A disc of filter-paper of 1 cm. diameter soaked in the test solution was placed on the skin of the volar aspect of the forearm under a light anode made of brass and perspex. A piece of filter-paper, soaked in 0·9% NaCl and wrapped round a copper plate, was firmly held between the thumb and forefinger and served as the cathode. The anode was held in position by light pressure, and ionization was carried out for 2 minutes in a draught-free room, with a 1 ma. current from a 50-volt battery. It was found that in order regularly to produce whealing with carbaminoyl choline it was necessary to use a solution at a dilution not greater than 1 : 100. It was also found that the skin reactions obtained with either solution were more prominent in the proximal part of the forearm, and for this reason tests with carbaminoyl choline (the milder whealing agent of the two) were carried out at approximately 5–6 cm. below the mid-point of the antecubital fossa. Those with histamine were performed within 6–7 cm. of the wrist. A few preliminary experiments showed that reversal of the sites of application of the two test solutions had no significant effect on the action of the anti-histamine drug, although, as stated above, the dimensions of the flare and wheal were invariably greater on the upper part of the forearm. In the early experiments histamine was used at a dilution of 1 : 100,000, but in order to show the effects of the anti-histamine drugs to better advantage a dilution of 1 : 1,000,000 was used in the later experiments. An attempt was also made to use concentrations of carbaminoyl choline and of histamine such as to give approximately equal skin reactions, but owing to wide individual variations it was not possible to obtain consistent results in the small number of subjects studied.

In order to determine the optimum time after ionization at which to measure the size of the flare and wheal, a number of tests were carried out in which measurements were made at 1 minute intervals up to 20 minutes after iontophoresis. It was found that the skin reactions to either histamine or carbaminoyl choline followed essentially the same course ; the flare and wheal both reach their maximum dimensions in about 5 minutes, and begin to decline approximately 10 minutes after ionization ; the reactions therefore were measured at approximately 7 minutes after iontophoresis of the test solution.

The anti-histamine drugs used in these experiments were mepyramine hydrogen maleate ("Anthisan," May and Baker) and promethazine hydrochloride ("Phenergan," May & Baker), which were taken orally in doses of

100 mg. and 25 mg. respectively. The drug was taken after initial readings had been obtained for both carbaminoyl choline and histamine. Further ionizations were carried out approximately 2 and 4 hours after taking the drug. A few experiments have also been done in which Anthisan cream (May & Baker) and an ointment and a cream incorporating 2-(N-phenyl-N-benzylamino-methyl)-imidazoline ("Antistin," Ciba) were rubbed into the skin of the volar aspect of the forearm. One gramme of the ointment (or cream) was thoroughly inuncted into the skin, and any excess was washed off after 20 minutes. The results obtained are not reported in detail here, but were approximately the same as those obtained when the drug was taken by mouth —allowance being made for the difference in dosage by the two routes.

Results.

Spread of Flare and Wheal after Ionization of Test Solutions.

Measurements were made of the size of the flare and wheal along two axes at right angles in five subjects at 1-minute intervals following ionization. These showed that both the wheal and the flare reached maximum dimensions within 4–5 minutes, with either solution and that these dimensions were maintained until at least 9–10 minutes after ionization. Results obtained with the two test solutions in one subject are given in Table I and may be regarded as typical.

The findings with ionized histamine agree closely with those of Lewis and Grant (1924) in their early work with histamine pricked into the skin. Iontophoresis possesses certain advantages over other methods of introducing histamine and other substances into the skin, in that wheal " pseudopodia " are not so commonly produced, so that usually there is no great difference between the two diameters chosen for measurements, thus eliminating a source of error which is difficult otherwise to assess. The same is not true, however, of measurements of the flare whose size depends upon many factors, not the least being the intimate anatomy of the cutaneous nerves at the site of ionization.

Effect of Oral Administration of Anti-histamine Drugs.

The effect of the oral administration of anti-histamine drugs on the skin responses to the test solutions were then studied in 18 subjects, and the results obtained are given in Tables II and III.

Discussion.

Grant, Pearson and Comeau (1936) made a careful study of six cases of so-called psychogenic urticaria in which the eruption was easily produced by emotional stimuli, exercise, warming the body or by the injection of various

TABLE I.—*Development of Wheal and Flare Produced by Histamine Hydrochloride* (1 : 1,000,000) *and Carbachol* (1 : 100).

(Measurement in mm. along 2 axes at right angles.)

Subject B.K.	Histamine 1 : 1,000,000		Carbachol 1 : 100.	
Time.	Wheal.	Flare.	Wheal.	Flare.
1 min.	10 × 12	20 × 22	9 × 10	Very faint
2 mins.	11 × 12	22 × 22	14 × 14	23 × 28
3 ,,	11 × 13	22 × 28	12 × 14	**26 × 28**
4 ,,	**12 × 13**	**30 × 31**	13 × 15	**26 × 29**
5 ,,	**12 × 13**	**30 × 31**	**14 × 14**	**25 × 28**
6 ,,	**12 × 13**	**31 × 31**	**14 × 14**	**25 × 28**
7 ,,	**12 × 13**	**30 × 31**	**14 × 14**	**25 × 28**
8 ,,	**12 × 12**	**30 × 30**	**14 × 14**	**24 × 28**
9 ,,	**12 × 12**	**30 × 30**	**14 × 14**	**25 × 28**
10 ,,	11 × 12	**30 × 30**	**14 × 14**	**24 × 28**
11 ,,	11 × 12	**30 × 30**	**14 × 14**	**24 × 28**
12 ,,	11 × 11	29 × 29	**14 × 14**	23 × 26
13 ,,	10 × 11	28 × 29	**14 × 14**	21 × 24
14 ,,	10 × 10	28 × 28	**14 × 14**	20 × 25
15 ,,	8 × 10	25 × 26	**14 × 14**	21 × 23
16 ,,	8 × 10	22 × 24	**14 × 14**	20 × 23
17 ,,	8 × 10	20 × 22	**14 × 14**	19 × 23
18 ,,	6 × 10	21 × 21	**14 × 14**	19 × 22
19 ,,	6 × 10	20 × 20	**14 × 14**	19 × 22
20 ,,	Vanished	16 × 20	12 × 14	18 × 22

cholinergic drugs. They came to the conclusion that the urticaria arises through stimulation of cholinergic nerves in subjects whose skin responds abnormally to a normal release of acetylcholine at the nerve endings. They considered that H-substance was released as a result of the abnormal acetylcholine response, and gave rise to the flare and wheal which produced the patients' symptoms. In their discussion they allude to the skin vasodilatation which follows antidromic stimulation of a sensory nerve, and refer to Lewis and Marvin's (1927) view that a stable vasodilator substance, probably H-substance, is released in the skin, although Dale (1933) and Wybau (1936) considered that the vasodilatation is due to a release of acetylcholine from the nerve-endings. Ungar, Zerling and Pocoulé (1935) support Lewis and Marvin's view, although Ungar (Ungar and Parrot, 1938) later modified his original view and considered that a third substance might be responsible. Brown (1937) suggested that the apparent discrepancy would appear to be due to the twofold nature of the sensory fibre, and would disappear if histamine

TABLE II.—*Effect of Anti-histamine Drugs* (100 *mg. Anthisan or* 25 *mg. Phenergan* per os) *on the Skin Reaction to Ionized Histamine Hydrochloride.*

(Measurement in mm. along 2 axes at right angles.)

Subject.	Drug.	Flare. Time in relation to administration of anti-histamine drug. Before.	After 2 hrs.	4 hrs.	Effect.	Wheal. Time in relation to administration of anti-histamine drug. Before.	After 2 hrs.	4 hrs.	Effect.
1. R. T—	Anthisan	60 × 46	50 × 50	31 × 24	+	17 × 15	17 × 14	13 × 12	+
2. M. O—	Anthisan	40 × 40	40 × 30	..	±	18 × 15	13 × 13	..	±
3. R. A—	Anthisan	58 × 53	45 × 45	45 × 45	+	17 × 16	15 × 15	15 × 14	−
	Phenergan	22 × 22	..	12 × 10	+	12 × 12	..	Practically *nil*	+
4. M. T—	Anthisan	40 × 26	35 × 35 (faint)	37 × 35	−	13 × 13 (flat)	12 × 10	11 × 8	±
5. R. B—	Anthisan	45 × 45	37 × 37	40 × 23	+	12 × 12	11 × 10 (very flat)	13 × 12	−
6. E. M—	Anthisan	35 × 28	20 × 20	25 × 20	+	13 × 11	10 × 8	10 × 10	+
7. D. W—	Anthisan	37 × 30	30 × 30	37 × 33	−	12 × 10	10 × 10	13 × 10	−
8. B. K—	Anthisan	32 × 22	..	11 × 11 (very faint)	+	14 × 12	..	11 × 11 (very flat)	−
	Phenergan	29 × 29	11 × 10	10 × 9	+	12 × 10	10 × 6 (flat)	*Nil*	+
9. E. S—	Anthisan	20 × 18	11 × 11	22 × 20	±	10 × 10	11 × 11 (flat)	10 × 10	−
10. A. T—	Anthisan	15 × 13 (faint)	6 × 5	11 × 10	+	12 × 12 (flat)	*Nil*	*Nil*	+
	Phenergan	10 × 8	..	12 × 10	−	10 × 8 (flat)	..	Almost *nil*	+
11. J. P—	Anthisan	35 × 20	32 × 25	50 × 40	−	11 × 11	13 × 12	12 × 12	−
12. I. J—	Anthisan	14 × 9	..	*Nil*	+	*nil*	..	*nil*	
13. C. J—	Phenergen	12 × 10	12 × 10	10 × 8	−	10 × 12	5 × 5	*nil*	+
14. G. S—	Phenergan	10 × 10	9 × 9	10 × 11	−	10 × 10	Pin-head	10 × 11	+
15. L. B—	Phenergan	32 × 37	12 × 12	10 × 15	+	10 × 9	*nil*	5 × 5 (?)	+
16. A. B—	Phenergen	12 × 10	18 × 14	10 × 8	−	10 × 5	10 × 6	Pin-head	+
17. J. B—	Phenergan	30 × 20	17 × 9	10 × 8	+	11 × 10	*nil*	*nil*	+
18. D. B—	Phenergan	21 × 25	13 × 13	17 × 13	+	13 × 10	Pin-head	Pin-head	+

+ = Definite reduction in size. ± = Slight reduction. − = No significant effect.

TABLE III.—*Effect of Anti-histamine Drugs* (100 *mg. Anthisan or* 25 *mg. Phenergan* per os) *on the Skin Reaction to Ionized Carbaminoyl Choline.*

(Measurement in mm. along 2 axes at right angles.)

Subject.	Drug.	Flare. Time in relation to administration of anti-histamine drug			Effect.	Wheal. Time in relation to administration of anti-histamine drug			Effect.
		Before.	After 2 hrs.	4 hrs.		Before.	After 2 hrs.	4 hrs.	
1. R. T—	Anthisan	48 × 36	32 × 20	31 × 24	+	12 × 10	5 × 5	8 × 8	+
2. M. O—	Anthisan	30 × 26	20 × 16	..	+	16 × 12	Almost *nil*	*nil*	+
3. R. A—	Anthisan	34 × 32	32 × 30	20 × 20	+	17 × 16	10 × 10	15 × 15 (flat)	+
	Phenergan	35 × 30	..	23 × 20	+	10 × 10	..	*nil*	+
4. M. T—	Anthisan	18 × 18	12 × 12	10 × 10	±	7 × 7 (flat)	*nil*	*nil*	+
5. R. B—	Anthisan	40 × 22	22 × 17	12 × 12	+	Almost *nil*	Pin-head	*nil*	−
6. E. M—	Anthisan	50 × 38	32 × 30	26 × 26	+	12 × 12	5 × 4	10 × 4	+
7. D. W—	Anthisan	40 × 38	35 × 25	35 × 30	+	18 × 14	10 × 9	11 × 11	+
8. B. K—	Anthisan	34 × 26	25 × 20	15 × 15	+	13 × 13	13 × 12	10 × 10	+
	Phenergan	29 × 25	19 × 17	16 × 17	+	15 × 14	12 × 13	12 × 13	−
9. E. S—	Anthisan	20 × 20	20 × 14	20 × 15	±	10 × 10 (flat)	10 × 10 (very faint)	12 × 10	−
10. A. T—	Anthisan	20 × 16	20 × 18	21 × 18	−	*nil*	*nil*	*nil*	
	Phenergan	20 × 18	..	14 × 13	±	10 × 10 (flat)	*nil*	*nil*	+
11. J. P—	Anthisan	38 × 34	40 × 30	50 × 30	−	11 × 11	10 × 7	15 × 15	−
12. I. J—	Anthisan	30 × 22	..	28 × 25	−	10 × 5	..	10 × 10	−
13. C. J—	Phenergan	22 × 15	12 × 13	12 × 11	+	5 × 5	Pin-head	*nil*	+
14. G. S—	Phenergan	25 × 22	15 × 13	20 × 20	+	11 × 11	Pin-head	Pin-head	+
15. L. B—	Phenergan	34 × 22	28 × 26	26 × 22	−	11 × 11	*nil*	Pin-head	+
16. A. B—	Phenergan	20 × 17	22 × 20	17 × 17	−	10 × 8	Pin-head	Pin-head	+
17. J. B—	Phenergan	25 × 20	25 × 20	20 × 20	−	10 × 10 (faint)	*nil*	*nil*	+
18. D. B—	Phenergan	38 × 34	35 × 31	40 × 34	−	13 × 13	12 × 13 (flat)	15 × 15	−

\+ = Definite reduction in size. ± = Slight reduction. − = No significant effect.

was, in fact, liberated at the true sensory ending, and if acetylcholine was released at the ending of the axon associated with the cutaneous arterioles. Another possible explanation, in the light of our present findings, is given below. In 1942 Parrot studied the effect of " 2339 R.P." on histamine skin wheals, and finding that they were suppressed following oral administration of the anti-histamine drug, concluded that the view held by Lewis and his collaborators was correct. It will be seen from our results that the suppression by an anti-histamine drug of wheals induced by a choline ester does not invalidate Dale's conclusion ; it is possible that both mechanisms are involved, and that the sequence may well be : antidromic stimulus —→ acetylcholine release at nerve ending —→ histamine release —→ vasodilatation.

The results presented here enable a comparison to be made of the ability of two anti-histamine drugs to modify the skin reaction to histamine and to carbaminoyl chloride. Owing to experimental conditions no reduction in the wheal size of less than 3 mm. in each of the two diameters measured was considered significant ; in the case of the flare a reduction of at least 10 mm. in one axis and 5 mm. in the other was required.

With these criteria in mind, a study of Tables II and III will show that an approximately parallel reduction in both wheal and flare for Carbachol and histamine was obtained in 7 subjects. In only one subject (No. 7) did the results seem to show a predominantly anti-cholinergic effect, and in another (No. 18) the measurements obtained appear to show a more pronounced anti-histamine effect. In one subject (No. 11) no significant reduction in the size of either wheal or flare was obtained for either Carbachol or histamine with the dosage of the anti-histamine drug taken, although it is possible that failure would have been avoided if he had been given a larger dose of mepyramine maleate. It should be noted that previous workers have also failed to obtain a reduction of histamine wheals in every case following oral administration of different anti-histamine drugs. Thus Arbesman *et al.* (1946) obtained wheal reduction in only 18 out of 28 subjects after oral administration of pyribenzamine.

From our results it may be concluded that the skin reactions following iontophoresis of either histamine or carbaminoyl choline can be reduced or suppressed following oral administration of an anti-histamine drug. In interpreting the mechanism whereby this is achieved, there can now be little doubt that as far as histamine is concerned, this is due to a competitive antagonism. It is now generally accepted that the anti-histamine drugs exert their action by blocking the cell receptor for histamine. However, many of these drugs possess an atropine-like property, and are able to prevent or depress the activity of acetylcholine and allied compounds.

This acetylcholine antagonism may be displayed in man by inhibition of salivary secretion (amounting to xerostoma in some patients), by mydriasis

and by their spasmolytic action (Loew, 1950). Not all anti-histamines possess this property, which is well marked in the benzhydryl ethers (*e.g.*, " Benadryl"), all of which closely resemble Transentin in their spasmolytic properties. However, neither of the drugs chosen for the present study can be said to possess this atropine-like action in any significant degree. Schild (1947) has estimated that the anti-acetylcholine activity of mepyramine maleate is only 1 : 40,000 of that of its activity against histamine. Similarly, Phenergan has an anti-acetylcholine activity of 1 : 36 compared with its anti-histamine activity, although its close congener Diparcol, which differs only in possessing an ethyl group instead of two methyl groups, has sufficient anti-cholinergic activity to find a place in the therapy of Parkinsonism, and is virtually devoid of anti-histamine activity. Therefore it is reasonable to conclude that the reduction or suppression of the skin reaction following iontophoresis of Carbachol by these drugs is due to their effect on histamine, and that " cholinergic " urticaria, both artificially induced and as seen in patients, is only indirectly due to cholinergic agents, histamine being released in the final stage.

It has recently been reported (Loewenthal, 1949) that Benadryl and Pyribenzamine give relief in all the cases of " cholinergic " dermatoses in which these drugs have been employed. Loewenthal favours the view that histamine release is responsible for the skin manifestations (urticaria and itching), but considers that proof of this is still unobtainable, even after the advent of the anti-histamine drugs. He mentions the anti-cholinergic action of Benadryl, but although abolition of the cutaneous manifestations in cases treated with Benadryl might be due to an anti-acetylcholine action, this could not be so with Pyribenzamine, whose action in this respect is negligible. Personal experience, limited to three cases of cholinergic urticaria, confirms Loewenthal's findings that the anti-histamine compounds are effective in controlling the eruption and itching in this malady.

Theoretically it would seem that drugs of the benzhydryl ether series, such as Benadryl, or those of the phenothiazine series, such as Phenergan, which possess activity against both histamine and acetylcholine, should prove more effective in the treatment of " cholinergic " urticaria. In this respect Diparcol, one of the phenothiazines, with proven clinical anti-acetylcholine activity, and with virtually no anti-histamine effects, would seem to be worthy of trial in these cases. In the one case in which it has been tried by the present author the urticaria was not influenced by this drug.

Since this work was completed a paper by Perry, Hosmer, and Sternberg (1951) has appeared which confirms our findings that the urticariogenic action of a choline ester can be modified or obliterated by the anti-histamine drugs. These authors, however, consider that these drugs have an " acetylcholine blocking " effect, but as Rothman (1951) states in his discussion of their paper,

and as we have mentioned above, the anti-acetylcholine activity of these drugs is probably insignificant and the predominant effect must be exerted *vis-à-vis* histamine.

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THE "L.E. CELL" AND ITS SIGNIFICANCE.

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THE purpose of this paper is to review the work that has been done on the demonstration of the " L.E. cell " in blood and bone-marrow preparations ; and after a brief description of six cases to consider its specificity, and its significance in the diagnosis and wider clinical concept of systemic lupus erythematosus.

Although anaemia and leucopenia have long been recognized as features of systemic lupus erythematosus, reports on bone-marrow examinations in this disease are difficult to find in the literature. Schaumann and Introzzi (1931), Bunim (1940) and Cluxton and Krause (1943) found no remarkable changes *post mortem*, while Ginzler and Fox (1940) looked particularly for evidence of necrosis and vascular changes but were able to find none.

In 1946 Hargraves began to study biopsy specimens of heparinized sternal marrow from these cases, and Morton (1947), working with him, described large round homogeneous purplish masses in the cytoplasm of polymorphonuclear leucocytes, and extracellular masses of similar material surrounded by normal polymorphonuclears. Although most of the intracellular bodies were homogeneous, a few showed a reticular pattern suggestive of nuclear structure. At the same time similar cells were noted by Sundberg (Haserick and Sundberg, 1948) in a typical case of acute disseminated lupus erythematosus, and in another patient without skin lesions, in whom the diagnosis of systemic lupus erythematosus had been considered on the evidence of history and laboratory findings.

These polymorphonuclear leucocytes containing a round homogeneous body were called " L.E. cells," and are to be distinguished (Hargraves *et al.* 1948) from somewhat similar cells which, in Hargraves's laboratory, came to be called Tart cells (from the name of the first patient in whom they were noticed). The Tart cell is a histiocyte with a " secondary nucleus " in which the chromatin, parachromatin and nuclear membrane can be detected. They may be found in heparinized marrow from patients with any serious disease and are without diagnostic significance.

Sundberg and Lick (1949) found L.E. cells in films made from the " buffy coat " of oxalated venous blood, but in smaller numbers than in bone-marrow preparations ; and Hargraves (1949), using venous blood, did not see L.E. cells as commonly as clumps of leucocytes surrounding extracellular basophilic masses. Hamburger (1950) used peripheral blood successfully, and Suksta

and Conley (1951) and Lee *et al.* (1951) have found it more satisfactory than bone marrow.

Haserick and Bortz (1949*a*, 1949*b*) produced L.E. cells by adding plasma from cases of systemic lupus erythematosus to heparinized normal marrow, and thus showed that their formation was due to some factor in the plasma rather than a fundamental change in the leucocytes. They referred to the formation of L.E. cells and basophilic material surrounded by rosettes of polymorphonuclear leucocytes (Fig. 1) as the "L.E. phenomenon," and considered it to be a specific test for acute disseminated lupus erythematosus. For routine use Haserick (1951*b*) finds dogs' marrow quite satisfactory, and although it rarely gives rise to L.E. cells, he considers that the extracellular masses and rosettes of polymorphonuclears are sufficiently characteristic for diagnostic purposes.

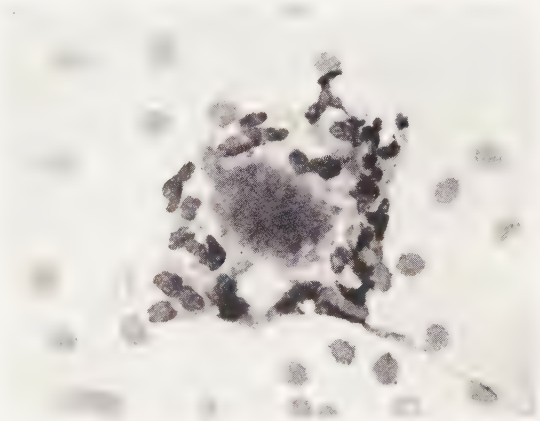

FIG. 1.—Clumping of polymorphonuclears around a mass of extracellular material. (× 675.)

To eliminate the difficulty of obtaining bone marrow, Moffatt *et al.* (1950) used instead the "buffy coat" of normal venous blood, and found it quite satisfactory for the demonstration of L.E. cells when lupus erythematosus plasma was added to it. In the hands of Moyer and Fisher (1950) and Haserick (1951*b*), however, this method was inconsistent and difficult to interpret.

Watson *et al.* (1951) were always able to demonstrate polymorphonuclear leucocytes resembling L.E. cells in scrapings from the floor of blisters made by the application of cantharides cerate to the skin of patients with systemic lupus erythematosus, and in several cases this method gave positive results where bone-marrow examinations had been negative.

L.E. cells can be found in the peripheral blood in the absence of an anticoagulant (Barnes *et al.*, 1950*a*; Conyea *et al.*, 1950), and Lee considers the examination of clotted venous blood the most sensitive method for the demonstration of the L.E. phenomenon.

In summary, preparations from four sources have been used to show the L.E. phenomenon in cases of systemic lupus erythematosus:

1. Heparinized bone marrow.
2. Peripheral blood, with or without an anticoagulant.
3. Plasma added to normal human or dog bone marrow.
4. Scrapings from cantharides blisters.

The Nature of the L.E. Body.

Although a typical L.E. body is a round, structureless, basophilic mass with a ground-glass appearance, enlarging the polymorphonuclear leucocyte and compressing the lobes of its nucleus against the cell membrane, some may have a granular or reticular appearance (Figs. 2 and 3) which suggests nuclear structure (Morton, 1947 ; Hargraves *et al.*, 1948). In the same marrow preparations Hargraves observed swelling and degeneration of some of the lobes of many polymorph nuclei, which became paler and gradually merged with the cytoplasm of their cells, and he thought that these degenerated nuclei either developed into L.E. bodies *in situ* or were extruded and later ingested by other polymorphonuclears. Barnes *et al.* (1950*b*, 1950*c*) described a small dark granular body in the cytoplasm of the *Hof* of a polymorph nucleus which they considered to be the first stage of the formation of the large homogeneous L.E. body. Although the great majority of L.E. bodies are in polymorphonuclear neutrophils, they are sometimes to be seen in eosinophils (Fig. 5) and in histiocytes.

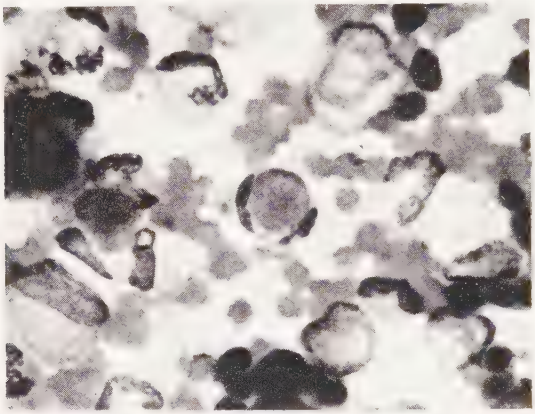

Fig. 2.—A round L.E. body showing some reticular structure, in a bilobed polymorphonuclear. (×675).

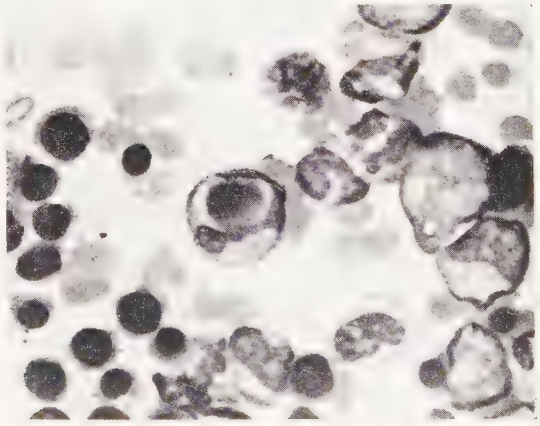

Fig. 3.—A homogeneous L.E. body in a young polymorphonuclear. (× 675.)

By applying plasma from cases of systemic lupus erythematosus to areas of exposed papillary layer of the forearm of human volunteers, after previous application of diphtheria toxoid or egg white to produce inflammation, Rebuck and Berman (1950) were able to watch the stages in the evolution of the L.E. phenomenon. After one hour there was swelling and gradual loss of chromatin pattern of one or more lobes of many of the polymorph nuclei : later the lobes became homogeneous, and either they were

extruded or the whole cell disintegrated, and finally the extracellular material was surrounded by intact polymorphonuclears and then ingested by them. As the material was digested it became paler until all that remained was the very faint blue of the nuclear membrane. In the control sites where only diphtheria toxoid or egg white had been used there was some evidence of phagocytosis of nuclear debris by lymphocytes and macrophages but not by polymorphonuclears. Nor did the addition of normal human plasma to prepared sites give rise to nucleolysis and phagocytosis by polymorphs.

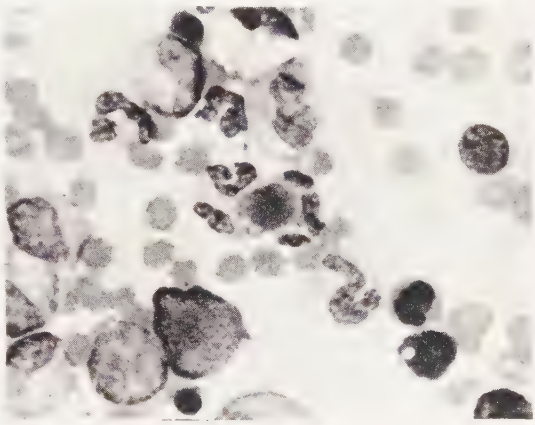

FIG. 4.—Polymorphonuclears ingesting extracellular material. (× 675.)

That the L.E. cell may be produced by phagocytosis of lymphocyte nuclei has been shown by Moyer and Fisher (1950), who added the " buffy coat " from a case of lymphatic leukaemia to a mixture of lupus erythematosus plasma and normal " buffy coat." The ingested bodies so produced in neutrophils varied from easily discernible lymphocyte nuclei to the amorphous masses typical of L.E. cells. The process was much more marked when the lymphocytes were first damaged by freezing. When a " buffy coat " rich in neutrophil leucocytes (from cases of acute infection) was used instead of that from lymphatic leukaemia, no L.E. cells were formed.

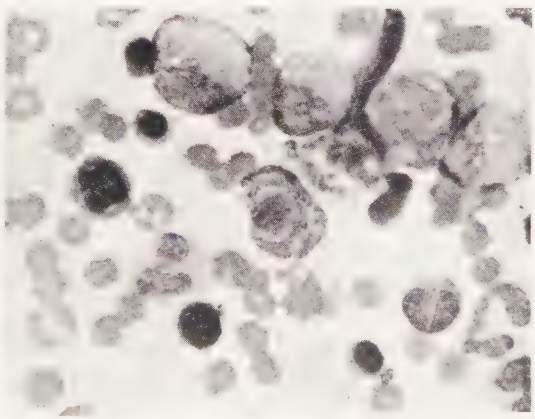

FIG. 5.—An eosinophil containing an L.E. body. (× 675.)

Lee *et al.* (1951) added lupus erythematosus plasma to the " buffy coat " from a case of lymphatic leukaemia and failed to produce L.E. cells. Using instead the " buffy coat " from a case of myeloid leukaemia there were a few L.E. cells but marked phagocytosis of red blood cells by polymorphonuclears —an interesting observation in view of Wiener's (1950) suggestion that the L.E. body might be an ingested erythrocyte. However, when the lupus erythematosus plasma was added

to a mixture of the "buffy coats" from both types of leukaemia there was dramatic phagocytosis of lymphocytes by granulocytes in all stages of maturity, and digestion to produce a final appearance identical with the L.E. body.

Histochemical and light-absorption studies indicate that the L.E. body consists of nuclear material of similar composition to that of the haematoxylin-staining bodies described originally by Gross (1932) in post-mortem preparations from cases of acute disseminated lupus erythematosus. Both are strongly Feulgen-positive and stain weakly with methyl green, indicating the presence of desoxyribose nucleic acid which is partly intact and partly depolymerized (Klemperer *et al.*, 1950; Lee *et al.*, 1951). While these workers report that the L.E. body stains red with the Unna-Pappenheim mixture, Berman *et al.* (1950) were unable to show that either the L.E. body or the extracellular material stained with pyronin.

The Serum Factor.

After Haserick and Bortz (1949*a*, 1949*b*) had produced the L.E. phenomenon in normal bone marrow by the addition of plasma from patients with systemic lupus erythematosus, they went on (Haserick, Lewis and Bortz, 1950) to show that the phenomenon could be induced by the serum globulin from these patients. That this is not a non-specific effect produced by the increased concentration of serum globulin has been shown by finding negative L.E. tests in other conditions associated with hyperglobulinaemia (Haserick, 1951*b*; Barnes *et al.*, 1950*b*). Further fractionation showed that only the γ-globulin is active, though quantitatively it is less effective than whole plasma (Lee *et al.*, 1951). In spite of the association of the L.E. serum factor with the γ-globulin the two are antigenically quite distinct, as Haserick and Lewis (1950) have shown in the following experiment: They prepared antisera in rabbits (*a*) to lupus erythematosus γ-globulin, and (*b*) to normal human γ-globulin. When these antisera were added to a solution of lupus erythematosus γ-globulin, precipitation occurred, and the supernatant fluid in the case of (*a*) was not capable of inducing the L.E. phenomenon in normal bone marrow, while in (*b*) it was. Further isolation of the serum factor has not yet been reported.

Hauser (1951) reports the case of a patient with systemic lupus erythematosus and marked signs in the central nervous system which raised the possibility of disseminated sclerosis. Although the usual tests on the cerebrospinal fluid were normal, the fluid was able to induce the L.E. phenomenon in normal marrow.

Haserick found that the serum factor is destroyed by bacterial invasion, and by heating to 65° C., but it is inactivated neither by storage for six months,

nor by the addition of cortisone or other steroids. In Case 2 of the present series the serum obtained at autopsy and stored in a refrigerator for two days was effective in inducing the L.E. phenomenon in normal marrow. Rabbit antisera to normal human plasma and to chronic lupus erythematosus plasma do not inactivate the serum factor, whereas the L.E. phenomenon is inhibited by antisera to plasma and to γ-globulin from cases of systemic lupus erythematosus.

Production of the "L.E. Phenomenon."

Since all the tests to demonstrate the phenomenon depend on bringing white blood cells into contact with lupus erythematosus serum, the absence of L.E. cells from the tissues—direct films of blood and marrow, and autopsy histological preparations –is a matter for speculation. In one case of systemic lupus erythematosus, Gueft (1950) found numerous haematoxylin-staining bodies but only one L.E. cell in sections of the marrow obtained at autopsy, and Schuermann and Hauser (1950) also found a single L.E. cell in an area of interstitial myositis occurring in a similar case. Many L.E. cells were found in pleural fluid by Van Doormaal and Schreuder (1950) shortly before death.

Early failures to confirm Hargraves's (1948) original observations were thought to be due to omission of heparin from the preparations, but it is now known that anticoagulants are unnecessary, though adequate time and a suitable temperature must be provided. Haserick (1950) stated that L.E. cells are found twelve minutes after mixing the plasma with normal bone marrow, but the formation of rosettes of polymorphonuclears around basophilic masses occurs earlier, while Lee *et al.* (1951) found some cells after two minutes, though the optimum time was 20 to 30 minutes. Suksta and Conley (1951) could not produce the phenomenon at 0° C. and found that at least 10 minutes elapsed at 37° C. before L.E. cells were seen, though extracellular masses were apparent after one minute.

It is significant that before L.E. cells are formed outside the body the plasma and white cells have been subjected to various kinds of trauma such as contact with the metal of a hollow needle, changes in temperature, centrifugalization—and that they are only formed in the body in the presence of an inflammatory reaction (e.g., from cantharides or pleurisy). It may be that the L.E. phenomenon is analogous to the clotting of blood, a process for which all the necessary constituents circulate in the blood-stream, yet which does not take place until some form of trauma, be it inflammatory, mechanical or thermal, liberates an enzyme from the platelets.

The phenomenon can also be induced in the marrow of monkeys, rabbits, rats and guinea-pigs, and Sundberg has found L.E. cells in the marrow of a rabbit twenty minutes after the intravenous injection of a large dose of lupus erythematosus serum (Berman *et al.*, 1950 ; Sundberg, 1950).

Methods for the L.E. Tests.

Although its technique is simple, the examination of films of the "buffy coat" of venous blood is not recommended as a routine method because a very lengthy search is usually necessary to find L.E. cells. If they are not found, an examination is made either of the patient's heparinized marrow, or of a mixture of the suspected plasma and normal bone marrow. The last method is preferable because not only does it avoid the somewhat traumatic procedure of marrow biopsy which may not be well tolerated in a patient who is very ill with acute systemic lupus erythematosus, but it may be more likely to show the L.E. phenomenon than other methods. Its one disadvantage is that specimens of normal marrow (i.e., from suitable patients who do not have systemic lupus erythematosus) must be readily available. In practice, any marrows, except those from leukaemias, pernicious anaemia and infective conditions, have been used satisfactorily.

Marrow biopsy.—The Schleicher modification of the Limarzi needle is used to obtain 1 c.c. of marrow from the ilium or sternum. The aspirated fluid is then put into a paraffin-coated tube containing heparin (Lot 152 made by Hynson, Westcott and Dunning). Marrow particles are removed for routine fixation, embedding and sectioning, and after the remaining fluid has stood at room temperature for at least 10 minutes it is placed in a Wintrobe haematocrit tube and centrifuged for 10 minutes at 1000 r.p.m. The surface layers of fat and plasma are then removed, and films are made from the myeloid-erythroid layer and stained with Wright's stain.

The Haserick rest.—To 1 c.c. of the patient's plasma is added 1 c.c. of normal heparinized bone marrow. The mixture is left at room temperature for at least 10 minutes before it is centrifuged and examined as before.

Case Records.

The following cases are described to illustrate the varying clinical pictures that may occur in patients with systemic lupus erythematosus who show the L.E. phenomenon, and to emphasize that the phenomenon is not detected by our present methods in every case.

Case 1.—A white girl, aged 14 years.

When admitted on 2 June 1950 she gave a nine weeks' history of joint pains, fever, loss of weight and a rash. She was acutely ill, with a temperature of 101° F. and a pulse rate of 100 per minute. She had crusted erythematous lesions on the nose and around the mouth, and haemorrhagic papulo-vesicular lesions on the extensor aspects of the forearms and legs. The lips and vulva were swollen, red and crusted. The clinical diagnosis was acute disseminated lupus erythematosus, and was supported by the following laboratory findings :

Urine : Albumin +. Occasional red cells.
Haemoglobin : 11·0 g. per 100 ml. E.S.R. (Westergren) 103 mm. in 1 hour.

W.B.C.: 2400 per c.mm. (neutrophils 63%, lymphocytes 32%, monocytes 5%).

Serum proteins: Albumin 1·6 g.; globulin 5·0 g. per 100 ml.

L.E. cells were found in the bone marrow.

The patient was treated with A.C.T.H. and discharged from hospital symptom-free at the end of 7 weeks, with only pigmentation at the sites of the old skin lesions. She was admitted four months later for a relapse, and died in March, 1951, with a terminal staphylococcal septicaemia. At autopsy abscesses due to Aspergillus were found in the brain and lungs.

Case 2.—An American Indian girl, aged 15 years.

For two years before this patient was admitted on 15 June 1950 she had had lupus erythematosus involving the face, arms and legs; the lesions first appeared in summer and were aggravated by sunlight. General symptoms of tiredness, fever, loss of weight and cough had been present for only the last six months, and had followed an attack of pneumonia. On admission she had a temperature of 101·6° F. and a pulse rate of 108 per minute. The skin lesions on the face had disappeared by that time, but the forearms and thighs showed pigmented atrophic areas. All the superficial lymph nodes were enlarged, and there were signs of consolidation at the base of the right lung. Laboratory investigations were as follows:

Urine: Albumin +. Occasional red cells.

Haemoglobin: 9·5 g. per 100 ml. E.S.R. (Westergren) 129 mm. in 1 hour.

W.B.C.: 11,450 per c.mm. (neutrophils 71%, lymphocytes 29%).

Serum proteins: Albumin 2·9 g.; globulin 5·1 g. (γ-globulin 2·1 g.) per 100 ml.

L.E. cells were found in the bone marrow, peripheral blood, and on the addition of serum to normal bone marrow.

She became afebrile in a few days and left the hospital after two weeks. Six months later she was readmitted with chest symptoms and a high fever, and she died in January 1951 with an acute staphylococcal septicaemia. The L.E. phenomenon was produced with the serum obtained at autopsy.

Case 3.—A white married woman, aged 39 years.

For two years this patient had had intermittent painful swellings of the knees, ankles and small joints of the hands, accompanied by fever, fatigue and loss of weight. She was admitted on 5 June 1950 with no fever and a normal pulse. There was a blotchy erythema, which faded on pressure, over the upper part of the thorax and breasts which was in no way suggestive of lupus erythematosus. The hands showed the changes of rheumatoid arthritis, which was the original clinical diagnosis. Laboratory findings were as follows:

Urine: No albumin and no red cells.

Haemoglobin: 10·4 g. per 100 ml. E.S.R. (Westergren) 106 mm. in 1 hour.

W.B.C.: 3350 per c. mm. (neutrophils 41%, lymphocytes 49%, monocytes 5%, eosinophils 4%, basophils 1%).

Wassermann reaction: Doubtful positive. V.D.R.L. test negative.

Serum proteins: Albumin 2·8 g.; globulin 5·2 g. (γ-globulin 2·3 g.) per 100 ml.

L.E. cells were found repeatedly in the peripheral blood, and on the addition of the patient's serum to normal marrow.

The general condition and joint pains were improved by cortisone, but a relapse of fever and joint symptoms brought her back into hospital for 6 weeks in October 1950. When last seen in the outpatient clinic in May 1951 she had been taking

cortisone by mouth since the previous November, in a dose that had been reduced to 37·5 mg. daily. There was still swelling of the hand joints and the E.S.R. was 91 mm. in 1 hour.

Case 4.—A white married woman, aged 29 years.

Symptoms of malaise, weakness, loss of weight and pain in the knees dated from the beginning of pregnancy 7 months before admission on 18 February 1951. She had had a spontaneous abortion in December 1950 and pneumonia in January 1951, which had been followed by attacks of nausea and vomiting. There had never been a rash. On examination she was cachectic, with a temperature of 101° F. and a pulse rate of 142 per minute. The skin was tight and pale over the hands and around the mouth, giving a suggestion of acrosclerosis. The cervical lymph nodes were enlarged. Laboratory investigations were as follows :

Urine : Albumin a trace. No red blood cells.
Haemoglobin : 10·1 g. per 100 ml. E.S.R. (Westergren) 86 mm. in 1 hour.
W.B.C. : 4400 per c. mm. (neutrophils 81%, lymphocytes 15%, monocytes 4%).
Serum proteins : Albumin 1·5 g. ; globulin 5·3 g. (γ-globulin 2·1 g.) per 100 ml.
Chest x-ray : Pneumonitis of the right middle lobe, with pleural thickening.
L.E. cells were found in large numbers in the bone marrow.

On treatment with A.C.T.H. she rapidly became afebrile, and gained 15 pounds in weight in 8 weeks. When last seen in May 1951 she was free of symptoms, with a haemoglobin of 13·7 g. and an E.S.R. of 84 mm. in 1 hour.

Case 5.—A white spinster, aged 44 years.

She had worked in a sanatorium for 20 years, but severe rheumatoid arthritis had greatly limited her activity since 1941. In 1949 she had had a bone graft for tuberculosis of the spine, and at that time tuberculous arthritis of the left knee had been diagnosed. For 6 months before her present admission on 15 August 1950 she had complained of loss of weight, fever, weakness and intermittent attacks of diarrhoea and vomiting, and in the last month or two she had developed scaly lesions on the hands and feet. On admission the temperature was 100° F., and the pulse rate 96 per minute. The skin showed well-defined, scaly, hyperkeratotic lesions on the finger-tips, thenar and hypothenar eminences, and on the soles. In places the scale had separated and left erosions. There was one similar lesion on the lobe of the right ear. The left knee showed swelling, crepitus, and limitation of movement. Laboratory investigations were as follows :

Urine : Albumin +. Red blood cells ++.
Haemoglobin : 10·8 g. per 100 ml. E.S.R. (Westergren) 92 mm. in 1 hour.
W.B.C. : 3000 per c.mm. (neutrophils 78%, lymphocytes 22%).
Serum proteins : Albumin 1·4 g. ; globulin 4·8 g. (γ-globulin 2·3 g.) per 100 ml.
Chest x-ray showed pneumonitis of the right lower lobe.
Biopsy of one of the finger lesions showed a histology compatible with lupus erythematosus.
L.E. cells were easily found in the bone marrow, and more easily in mixtures of plasma and normal marrow. None was seen in the peripheral blood.

The temperature fell to normal after a few days of A.C.T.H. therapy, but the sedimentation rate, white count and urinary findings were persistently abnormal. The arthritis of the knee became worse during treatment, and tubercle bacilli were cultured from the urine. The patient was transferred to a sanatorium, with a diagnosis of tuberculosis of the kidney and knee, and lupus erythematosus.

Case 6.—A Philippine man, aged 48 years.

Malaise, loss of weight, joint pains and skin lesions had been present for 6 months before he was admitted on 31 August 1950. At this time he presented typical erythemato-squamous lesions of lupus erythematosus in a " butterfly " distribution on the face, and on the forehead, neck and sides of the fingers. The temperature was 100° F. and the pulse rate 120 per minute.

Urine : Albumin a trace. No red cells.
Haemoglobin : 12·7 g. per 100 ml. E.S.R. (Westergren) 62 mm. in 1 hour.
W.B.C. : 2300 per c.mm. (neutrophils 81%, lymphocytes 13%, monocytes 5%, eosinophils 1%).
V.D.R.L. test negative.
Chest x-ray : Pneumonitis of the right lower lobe.
Examinations for L.E. cells were repeatedly negative.

There was subjective improvement and a cessation of fever when this patient was treated with A.C.T.H. and cortisone, and when he was discharged on 1 November 1950 the skin changes were of residual hyper-pigmentation only, although his general condition was not yet normal. He was last seen in the out-patient clinic in May 1951 and the pigmentation had practically gone, but he was still an invalid and complained of some chest pain. The haemoglobin was 17·0 g.%, the E.S.R. 14 mm. in 1 hour, and the leucocyte count 6100 per c.mm.

Discussion.

The first five cases are representative of those reported in the literature as showing the presence of the L.E. phenomenon, while the sixth showed all the clinical and laboratory features of systemic lupus erythematosus, but had repeatedly negative tests. Cases 1 and 2 could reasonably be called acute disseminated lupus erythematosus in that both were fatal within a year of the onset of systemic symptoms, which in the second case only were preceded for eighteen months by the lesions of disseminated cutaneous lupus erythematosus. In Case 3 there was a two-year history of arthritis of the rheumatoid type as well as loss of weight and an ill-defined erythema of the chest ; and Case 4 had a similarly vague history in which vomiting and diarrhoea were prominent. If the L.E. cell had not been demonstrated, almost certainly the diagnosis would not have been made in these cases, and perhaps some dermatologists will still question it in the absence of cutaneous lesions. However, in view of the specificity of the L.E. tests it seems reasonable to accept that diagnosis here, with the reservation that in future cases of a similar nature systemic fungus infection must most carefully be considered (*vide infra*).

Case 5 is doubly interesting in that it illustrates the occurrence of lupus erythematosus in the course of active non-pulmonary tuberculosis (an association that is very rarely observed in the United States), and furthermore, the skin lesions were of the warty hyperkeratotic type that has long been considered by Barber (1950) to be suggestive of a past or present tuberculous infection. Clinically, Case 6 presented an obvious diagnosis which was supported by laboratory investigations, but repeated examinations failed to show L.E.

cells. No reason can be given for this observation, of which there are 7 other instances in cases of acute disseminated lupus erythematosus reported in the literature.

The following table correlates the finding of L.E. cells with the various types of lupus erythematosus reported in the last four years :

In the control series most workers have paid particular attention to the so-called collagen diseases, dermatomyositis, scleroderma and polyarteritis nodosa ; rheumatic fever and rheumatoid arthritis ; blood and renal diseases and hyperglobulinaemias due to cirrhosis, myelomatosis, lymphogranuloma inguinale, and sarcoidosis ; but in none of these conditions has the L.E. phenomenon been demonstrated. Since a history of epileptic fits was prominent in some of Haserick's cases, Weiss (1950) performed tests with the plasma of four epileptics under treatment with mesantoin (3-methyl-5, 5-phenylethylhydantoin) and obtained negative results. In regard to Gold's (1951) recent discussion on the part played by penicillin and the sulphonamides in the causation of systemic lupus erythematosus, it is interesting to note that the plasma of 11 cases of sensitivity to various drugs (including sulphonamides, gold, horse serum and penicillin) failed to produce true L.E. cells, though Tart cells and polymorphs with ingested red blood cells were seen (Suksta and Conley, 1951).

Only five positive tests were obtained in over 350 of the control series, and it is worth while to examine them more closely. The first was in a case originally diagnosed as myelomatosis (Montgomery and McCreight, 1949), but in which this diagnosis has since been seriously doubted (Hargraves, 1951). Lee *et al.* (1951) mention that Kurnik demonstrated the L.E. phenomenon in a patient who was found at autopsy to have miliary tuberculosis, and they also cite a case of acute haemolytic anaemia in which the tests were positive, though the spleen removed at operation showed no histological evidence of lupus erythematosus. Again, these authors found in the marrow of a patient with primary amyloidosis a single cell identical with an L.E. cell when stained by the Jenner-Giemsa method, but Feulgen-negative, and undoubtedly containing amyloid. Berman *et al.* (1950) found L.E. cells in very small numbers in one case each of pernicious anaemia in relapse, in dermatitis herpetiformis, and in lupus erythematosus of both the chronic discoid and chronic disseminated types, but they pointed out that the cells were not more numerous than 1 per 500 neutrophils, whereas in systemic lupus erythematosus the smallest number was 9 per 500 neutrophils. They felt that even if the test were not qualitatively specific, it was quantitatively of great value.

Haserick's recovery of *Aspergillus niger* (1951*a*) from the plasma of a patient diagnosed clinically as systemic lupus erythematosus, and his subsequent production of the L.E. phenomenon by adding a small quantity of the fungal

	Acute.		Acute and subacute.		Systemic, without skin lesions.		Subacute.		Chronic disseminated.		Chronic discoid.		Controls.	
	Total.	L.E.+.	Total.	L.E.+.	Total.	L.E.+.	Total.	L.E.+.	Total.	L.E.+.	Total.	L.E.+.	Total.	L.E.+.
Morton (1947)	..	..	8	5	2	2	..	..	1	0	..	..	20	0
Haserick and Sundberg (1948)	5	4	..	..	1	1	2	0	..	..	3	0	?	0
Montgomery and McCreight (1949)	6	5	..	..	..	..	17	3	1	0	..	..	?	1
Vilanova and DeDalelanto (1949)	2	1	..	..	..	..	..	..	..	..	..	..	..	..
Berman *et al.* (1950)	4	4	..	..	..	..	1	1	1	1*	1	1*	10	2*
Barnes *et al.* (1950*b*)	17	17	..	..	..	..	20	6	2	0	3	0	92	0
Madden (1950)	8	4	..	..	..	..	6	0	..	..	..	..	6	0
Suksta and Conley (1951)	..	..	21	14	..	..	..	..	..	..	5	0	89	0
Lee *et al.* (1951)	18	17	..	..	..	..	..	..	..	..	..	..	?	2
Haserick (1951*b*)	..	..	13	13	10	10	..	..	..	..	7	0	88	0
Watson *et al.* (1951)	5	5	12	12	..	..	..	..	..	..	6	0	53	0
Smith, present series	..	..	4	3	2	2	..	..	..	..	..	..	..	..
	65	57	58	47	15	15	46	10	5	1*	25	1*	358+	5

L.E.+ indicates the presence of the L.E. phenomenon.

* One L.E. cell per 500 neutrophils.

culture to normal serum and dogs' marrow, give rise to considerable speculation. Other isolated observations add more interest to this finding. The only one of a series of 14 cases of systemic lupus erythematosus that failed to respond to steroid therapy showed at autopsy an extensive fungus infection of the lungs (Soffer *et al.*, 1950). Similarly Case 1 of the present series developed a terminal staphylococcal septicaemia that failed to respond to antibiotics, and was found *post mortem* to have abscesses of the brain and lungs containing mycelium and spores of aspergillus. Finally, one L.E. cell was reported by Gausewitz *et al.* (1951) in the marrow of a patient with systemic moniliasis.

With one exception (Berman *et al.*, 1950), all workers are agreed that the L.E. phenomenon cannot be demonstrated in cases of chronic lupus erythematosus without systemic manifestations. Similarly, there is agreement that in the acute systemic type it is unusual not to find the L.E. cell, and the more ill the patient the more obvious the phenomenon, while in spontaneous remissions it is likely to be diminished or absent. After treatment with A.C.T.H. or cortisone it may disappear temporarily, but just as the leucopenia and the elevated E.S.R. remain, so is the L.E. phenomenon always present at some time or other (Baehr and Soffer, 1950; Brunsting *et al.*, 1951). In subacute cases the results are less consistent because of the varied connotation of the term in the hands of different observers, which is inevitable so long as cases are placed in this group mainly because they do not appropriately fit into the acute systemic or the chronic cutaneous groups. Some of them are probably of the discoid type with vague general symptoms of unrelated origin; others, still purely cutaneous, show much more temporary lesions and are very suitably described by Michelson (1951) as the acute oedematous localized type; a further group is represented by the acute systemic type in remission, and finally there are those represented by Cases 3 and 4 of this series, which Michelson has described as protracted systemic lupus erythematosus. Only this last type, characterized by a chronic debilitating illness with anaemia, joint pains and episodes of inflammation of the serous membranes, is likely to give rise to L.E. cells, and indeed their presence is the only sure way to make the diagnosis.

It would be convenient to be able to divide lupus erythematosus, by the presence or absence of the L.E. phenomenon, into two main categories, systemic and cutaneous; but on clinical and serological grounds this would almost certainly be an artificial division. In the first place the value of the L.E. tests in their present form is diminished by the fact that some undoubted cases of acute systemic lupus erythematosus do not give rise to the L.E. phenomenon; secondly, it is well known that an occasional chronic discoid case, often after injudicious therapy, may become acute and fatal; and finally there is the problem of the elevated serum γ-globulin (Walker and Benditt, 1950) and erythrocyte sedimentation rate in many chronic cases in

good health. Cochrane (1951) has suggested that the raised E.S.R. is an indication of poor prognosis *qua* cutaneous lesions, but one would like to know if it might be an index of latent or potential systemic involvement, and whether it is related to the γ-globulin level and the incidence of false-positive tests for syphilis which are known to occur in this disease, and yet which do not necessarily reflect systemic manifestations (White, 1947).

Conclusions.

The important work begun by Hargraves and extended by Haserick and others is the most valuable contribution to our knowledge of systemic lupus erythematosus since the observations of Libman and Sacks (1924), whose belief that their cases of atypical verrucous endocarditis were examples of lupus erythematosus was not shared by others at that time. Now the demonstration of the L.E. serum factor in the protracted systemic type of the disease, with or without skin lesions and endocarditis, enables us to diagnose a condition which previously must often have remained unrecognized. The demonstration of the L.E. phenomenon has helped to direct attention from the organic anatomical alterations in various organs and systems, and to emphasize Klemperer's (1938) belief that they are only the effects of some more fundamental process. What this is we still do not know, nor do we understand the relationship of one form of lupus erythematosus to another, and its relationship with other diseases of collagen. The absence of the L.E. cell from other members of that group of diseases helps to preserve the identity of systemic lupus erythematosus, but on the other hand the detection, in many cases of lupus erythematosus and rheumatoid arthritis, of another serum factor which agglutinates sensitized sheep's red blood cells suggests that there may be some relationship between these two conditions (Svartz, 1950; Ball, 1950).

More widespread use of the L.E. tests has probably been prevented by the difficulty of obtaining specimens of bone marrow, but if the method using clotted blood which Lee (1951) found so satisfactory proves to be as successful in the hands of other workers, it is to be hoped that repeated tests will be done in all types of lupus erythematosus, and in many other conditions, with particular reference to systemic fungous infections, tuberculosis, streptococcal infections and drug sensitivities.

Summary.

The morphology, methods of production and specificity of the L.E. cell are reviewed. It is a polymorphonuclear leucocyte which, in the presence of a factor associated with the serum γ-globulin, contains a round homogeneous mass of ingested nuclear material which gives staining reactions identical with those of the haematoxylin-bodies found in the viscera.

The demonstration of the L.E. cell may be regarded as a specific test for systemic lupus erythematosus.

Five cases are presented to show the clinical types of the disease that give rise to the L.E. phenomenon, and to draw attention to the protracted systemic form in which cutaneous lesions may be absent. The sixth case illustrates the fact that with present methods it is not always possible to demonstrate the phenomenon in undoubted cases of acute systemic L.E.

Negative tests are always obtained in other diseases—notably the so-called collagen diseases, various hyperglobulinaemias, and many other conditions.

Two cases in the series, and several reports in the literature, call attention to the possible connection between systemic lupus erythematosus and tuberculosis and the deep mycoses.

For his encouragement and help I thank Dr. Henry E. Michelson, Director of the Division of Dermatology, University of Minnesota; and for her kind co-operation I am indebted to Dr. R. Dorothy Sundberg, in whose laboratory the haematological work was done. I am most grateful to Miss Harriette Broman, who made the blood and marrow preparations and gave me much help in interpreting them.

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ROYAL SOCIETY OF MEDICINE.

SECTION OF DERMATOLOGY.

President : Dr. W. N. Goldsmith.

15 March 1951.

Congenital Papillomatous Ichthyosiform Ectodermal Defect : Treatment by Hypnosis.—Dr. S. A. Mason.

J. H—, aged 15½.

History.—According to his mother, this patient was born with a thick skin, which has progressively become thicker and darker throughout his life.

He was seen as an infant at several London hospitals but treatment was interrupted owing to the war and subsequent evacuation.

After the war he was again seen at two London teaching hospitals amongst others. Various treatments, the details of which have proved difficult to ascertain, were tried but to no avail.

The boy suffered much mental distress because of his appearance and also because of the unpleasant smell of his entire body surface.

In desperation he was referred to East Grinstead Plastic Unit and was admitted there on 5.ix.50 under the care of Mr. F. T. Moore, so that an attempt might be made to graft the areas of his body with unaffected skin, which he had on his chest only.

Treatment.—Treatment was commenced on the palms, on which he had dermatome grafts from his chest. Before the grafts had even healed properly, a similar warty condition occurred on them. These were diathermized but they recurred time and again.

At the first dressing ten days after grafting the grafts appeared abnormal in that they presented an ichthyotic appearance. After a period of a few weeks they looked exactly similar to the ichthyotic skin on the rest of his body. The patient was seen in consultation with other plastic surgeons, who agreed that further grafting operations were unlikely to meet with any degree of success but could suggest no alternative method of treatment.

10.ii.51.—Patient was hypnotized and told that the skin of his left arm would become normal. (The left arm only was suggested so as to obviate any chance of coincidental healing.) After five days, the patient noticed some improvement and after seven days this became obvious. The right arm was then treated in the same way, and ten days later the legs were treated.

The warty condition has improved rapidly, and the limbs show gradation of improvement according to the length of treatment. Improvement occurs first on the areas of friction and pressure and later on the rest of the skin.

Along with the improvement of his skin has gone a great mental improvement, and for the first time for many years the patient is not afraid to be seen and to mix with other people. The smell has vastly lessened, and further improvement will no doubt occur when the condition has completely cleared up.

Biopsy of the skin of his calf was taken under hypnosis on 27.ii.51 and sent for section to Prof. H. A. Magnus, of King's College Hospital. The report is :

> "Section shows a massive degree of hyperkeratosis, the average thickness of the keratin layer being 1·5 mm. The keratin is laminated and has produced many fissures in the underlying epidermis, which is atrophic. There is no parakeratosis. A thin granular layer is present. There are no changes in the

corium, apart from a marked deficiency in elastic fibre, only occasional fragments of which are present.

"This histological picture is similar to that described as being present in ichthyosis congenita."

The case is interesting because of the speed of improvement under hypnosis when all other forms of treatment had failed. The gradation of improvement is also of interest, and followed strictly the suggestions made under hypnosis.

Dr. A. C. Roxburgh : Is there any other chronic dermatological condition which Dr. Mason has so far cured by the same method ?

Dr. Mason : I have treated one case of neurodermatitis. The neurodermatitis extended as far as the patient's eyes, and he developed a corneitis and subsequent corneal opacity. He was having lamellar grafts done, but these failed repeatedly because they became infected due to the patient constantly rubbing his eyes. The patient had intense generalized pruritus which was not relieved by sodium amytal 60 grains daily. He also slept very poorly.

The patient was hypnotized and told that the itching would go. He improved immediately and after six treatments was taken off amytal. He was discharged considerably improved.

I also had a case of confluent psoriasis referred to me. I hypnotized him (he was very difficult to hypnotize), and suggested that the condition would clear up and get better. Four days later he came back to me very excited and said that the psoriasis had started to go from his hands and chest, this being the first improvement for some 20 years. He has since steadily improved. I hope to show him later.

I have treated cases of idiopathic pruritus and ordinary warts very successfully ; I think the warts were invariably cured.

I have also treated a case of cheiropompholyx that had resisted all forms of medication. I suggested that the itching would disappear. This was so immediately, and the actual cheiropompholyx went after about six days. I am aware that the natural tendency of this condition is to clear up spontaneously. I have found, however, that skin conditions that are accompanied by itching tend to heal if the itching alone is removed.

Dr. Whittle : I should like to ask whether Dr. Mason has had any experience of hypnotizing babies, or if it is possible to do so.

Dr. Mason : I find that the ease with which one can hypnotize depends to a great extent on the age of the patient. The younger the patient the easier they are to hypnotize. We often use hypnotism for the troublesome child who will not take an anaesthetic mask ; the child is hypnotized and then takes the mask quite readily. However, below the age of five or six a child does not co-operate, and as it is never possible to hypnotize an unco-operative patient, I do not think babies could be hypnotized.

Dr. Wilkinson : Results in certain dermatological cases are achieved by psychotherapy. Hypnosis has been used in the past on many occasions, It has certain definite indications, and it seems to be successful, especially in short-term results in certain conditions. The case which Dr. Mason has shown is really most astonishing, in that it is a naevoid condition which has responded to hypnosis. This opens up a much wider field than we had thought about before.

Dr. H. J. Wallace : I should like to ask Dr. Mason how much irritation and scratching occurred in this patient's skin.

Dr. Mason : He has very slight irritation around the areas of exfoliation of the ichthyotic condition. The skin reddens a little and he scratches a little. This irritation does not keep him awake and there are no visible excoriations.

Dr. Wallace : Do you think that any of the good effect of hypnosis is referable to the lessening of irritation produced by hypnosis ?

Dr. Mason : Not in this patient, because he had almost no irritation to begin with, and if anything he has had a little more irritation since. He used to have irritation when an area became infected, but an uninfected area did not irritate.

The President : Have you any theory about the mechanism of localization, in cases in which you produce or banish lesions in specified areas by suggestion ?

Dr. Mason : I have produced lesions in hypnotized persons by touching the arm with an ordinary spoon and saying that it is red hot. The person jumps, and an area of erythema and sometimes vesiculation appears a little later. I cannot give any certain explanation for it, but it may be due to local vasospasm and histamine liberation.

Dr. Forman : Has Dr. Mason noticed any change in the amount of sweating after treatment. I can imagine that sweat might soften the horn and allow its easy removal. At the moment the skin which is free of horn is still thickened.

Dr. Mason : I have not noticed any change in the boy's sweating (it is a difficult observation to make), but I noticed when he first came to me that his smell was appalling. That smell is now almost absent. Whether that has any bearing on the actual sweating I do not know, but under hypnosis I can make a patient sweat.

Dr. Forman : In any particular area ?

Dr. Mason : I do not know, but one can cause generalized sweating by suggesting heat or fear.

Dr. R. D. Moyle : Some weeks ago I saw the patient whom Dr. Mason has shown to-day. The left arm was then clear of the warty tissue but the skin was certainly much thickened. When I saw him again two weeks ago at a medical meeting at East Grinstead there was less thickening, and as I see him to-day there is still less thickening. When I first saw him the skin was almost like a fibrous tissue, but now it has not that feeling at all.

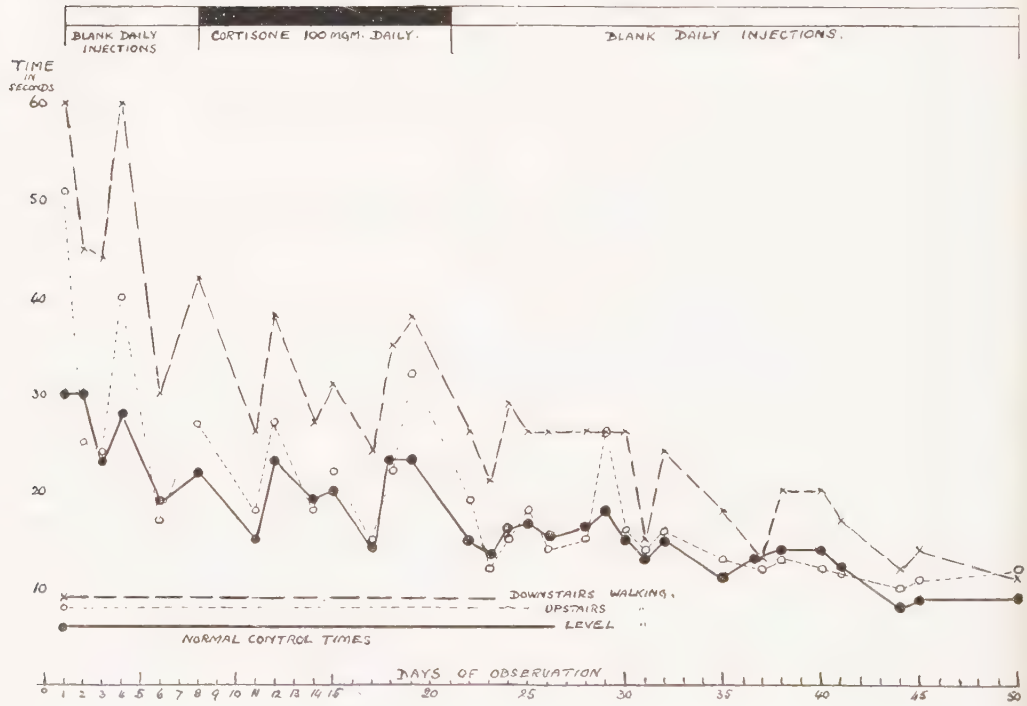
Dr. H. T. Wilson : A hypnotist I know (a physician who does hypnosis occasionally) obtained the best results in children between the ages of 5 and 10 years. I asked him to treat a series of children with warts, the number of warts varying from ten or twelve to fifty, and in twelve cases out of twenty they cleared completely. We had one with over fifty warts which disappeared in two or three weeks, and in another eighteen plantar warts went in a week. Other cases were no better after quite a long series of sessions. Two cases of lichen simplex in children cleared up, and two cases of atopic eczema improved significantly. Both the latter were children whose eczema was, I thought, tending to clear, but who kept it going by continuous scratching.

In no case of warts cured by hypnosis did the warts recur. After all other treatments I have found that a proportion of apparent successes later relapsed.

Cortisone Treatment in a Case of Generalised Scleroderma with Sclerodactyly and Dermatomyositis.—Dr. C. H. Whittle.

Miss L. F—, aged 36 :

First seen 29.iii.50 with 10 months' history of generalized symmetrical scleroderma with sclerodactyly, which started in the fingers. Deadness and coldness



gave place to loss of power. The face and eyelids became swollen at one period. There were muscle pains in the legs with subsequent difficulty in walking upstairs. Anorexia and vomiting were prominent features. Her limbs and trunk were then wasted and the skin pigmented.

Admitted to the ward 6.iv.50. Irregular fever persisted for two or three weeks with active symptoms (E.S.R. 37 mm.) dysphagia and occasional vomiting. Her face was mask-like and she smiled with difficulty. The muscles were involved as

well as the skin. The skin of the hands was stiff, shiny, atrophic and inelastic, and the musculature of the limbs and trunk was wasted.

Special investigations.—Biopsy of skin (R. forearm): Histological changes of scleroderma.

E.S.R.: 37 mm., or less (corrected figure).

Barium swallow and meal: No evidence of visceral disease.

Skiagram of hands: No rarefaction or calcinosis present.

Blood count: Normal.

Urinary creatine: 0·15-0·21 g. per litre.

Treatment.—Symptomatic. Priscol was useless.

Course.—Little change over several months.

Cortisone treatment.—6.xii.50: Readmitted to ward for cortisone treatment. She was put on to standard walking exercises daily (*a*) up stairs, (*b*) down stairs, (*c*) on the level, and the times taken were recorded. The exercises were carried out daily, or every two or three days, for seven weeks, and the increase in speed noted.

She was given a series of blank intramuscular injections daily for a week and the injections were then changed to 100 mg. of cortisone, daily injections for a fortnight; thereupon blank injections were again given daily till the end of the period of observation. Great care was taken to disguise the blank injections. Cholesterol emulsion indistinguishable in appearance from cortisone was put up in cortisone bottles, and no one but the dispenser knew when the changes from blank to cortisone and back were made.

There has been steady improvement in her power and mobility since the treatment was started: there has also been improvement in symptoms. But the cortisone did not appear to influence the rate of progress in any way.

The chart shows increased speed in performing standard walking exercises, irrespective of whether cortisone was given or not. Grip pressure measurements (Quin, Mason and Knowelden, 1950) were tried but found unsatisfactory for this case.

Failure to respond to cortisone may be attributable to the phase of the disease, which showed diminishing activity.

REFERENCE.

QUIN, C. E., MASON, R. M., and KNOWELDEN, M. J. (1950) *Brit. med. J.*, **2**, 810.

Dr. ALICE CARLETON: I saw a case of scleroderma which had been treated in the U.S.A. with cortisone. She had had four full treatments, and she told me that three days after the course was finished she began to feel stiff again, and at the end of a fortnight she was no better than she had been before the treatment was started.

Dr. SOMMERVILLE: In a series of cases treated with a cortisone-like substance—H. P. C. – one case was very similar to that described by Dr. Whittle. I have not seen the patient recently, because she was not my own patient, but we came to the conclusion that she had hardly responded to the treatment.

The PRESIDENT: One sometimes sees a quite dramatic drop in the creatine excretion in the first few days after the patient comes into hospital.

Primary Tuberculosis of the Skin.—Dr. D. E. SHARVILL (for Dr. SYDNEY THOMSON.)

A girl, aged 20 months.

A "pimple" appeared on the upper lip in October 1950 which ulcerated after two weeks, then improved with ointment. The parents and the family doctor considered this to be a septic spot and did not worry about it.

In February 1951 a lump appeared in the neck for which specialist advice was sought. The surgeon suggested the tuberculous nature of the gland and sent the child to the E.N.T. surgeon, who considered the tonsils normal, and also to the Skin Department.

Family history.—Grandfather, who lived in the same house, died one month ago of pulmonary tuberculosis ; he was fond of the child and frequently kissed her. An uncle also has pulmonary tuberculosis. The parents' chests are radiologically normal.

On 28.ii.51 there was a slightly raised lesion on the upper lip $\frac{3}{4}$ in. by $\frac{1}{2}$ in. of dusky erythematous colour. The surface was smooth and the edges sharply demarcated. At first sight there was little specific in its appearance, but on diascopy several areas of an apple-jelly colour were evident. There was a firm painless gland of pea size under the right mandible, not fixed to the skin or deep tissue.

A tuberculin jelly test was strongly positive. Chest skiagram was normal.

On March 7 the skin lesion had lost its erythematous colour, and a few outlying yellowish follicular papules had appeared.

The gland, however, had greatly increased in size and was fluctant, with red scaly overlying skin. It was aspirated, and large numbers of acid-fast bacilli found. The skin lesion was scraped gently and material examined directly, with negative result. Culture and guinea-pig inoculation were also negative.

Now the skin lesion is smaller and of less frankly tuberculous appearance, and the gland is subsiding.

No treatment has been given, except aspiration of the gland.

Dr. L. Forman : There seems to have been an unusually long period of time—four or five months—between the appearance of the ulcer on the lip and the gland. These cases are very rare.

Dr. R. E. Bowers : I saw a child, aged 2, with an ulcer on the side of the face. There was a neat little chain of lupus nodules along the lymphatics between the ulcer and the gland. With calciferol the condition cleared entirely. She was observed for about three years afterwards.

Dr. J. Sommerville : During the last eighteen months we have had two cases at the Western Infirmary, Glasgow, that were distinctly comparable with Dr. Sharvill's case, going through the same processes, and both cleared up with calciferol treatment.

Dr. D. S. Wilkinson : A child developed a similar primary lesion at the age of about 3 months. First there was an ulcer, and then the cervical gland became large and soft and aroused our suspicions. We treated the child with calciferol. In another the lesion began as soon as the baby had left the nursing home.

The President : Do paediatricians and chest physicians usually leave these cases untreated ? I was rather surprised to hear that they generally cleared up.

Dr. D. S. Wilkinson : I think the practice varies. They like to keep young children under observation ; and the older children are treated with streptomycin.

The President : I had a case in a child aged 2, in which the tuberculous chancre, which was on the scalp, continued to extend during a period of six months. It was not until after calciferol treatment was started that the lesion began to heal. After eight weeks' treatment it had healed completely.

Dr. D. I. Williams : Primary tuberculosis affecting the lung usually clears up unnoticed and it seems reasonable that spontaneous cure might also happen in the case of the skin. I can understand that the parents may demand that something should be done and it may be reasonable to give calciferol ; but I should be a little afraid of giving streptomycin in a case where the child was happily building up his immunity ; the immunity might be destroyed, and should the disease become generalized one would not have this very useful weapon to employ. I should be opposed to the immediate use of streptomycin, but I might use calciferol.

Dr. F. R. Bettley : I agree that a large proportion of these cases clear up, but some of them develop very serious pulmonary disease. I should be unhappy to see this child not treated. There is no good evidence of localization, and I think it would be wrong to withhold treatment when the child may be faced with a fatal spread of the disease.

Dr. J. Overton : I know of no one who has had any consistent success in the use of para-aminosalicylic acid either locally or by mouth for skin tuberculosis. I have tried it repeatedly without any success. With regard to the question of immunity and the use of streptomycin I know of no satisfactory evidence to show that the giving of this antibiotic reduces the tendency to develop immunity.

Keratosis Pilaris Associated with Myxoedema.– Dr. Louis Forman.

Miss V. J—, aged 14.

Complaint of dryness of the skin of the body, limbs and hands for two years. Periods commenced at 13 years. During the past year she has lacked energy and

has put on weight for three years. She feels the cold badly and the appetite is poor. The maternal grandmother had myxoedema.

Her face is pale, rounded and heavy lidded. The nose is broad, probably due to an old injury. The scalp hair line is set well back at the temples. The lanugo hair over the back and cheeks is thickened and dark.

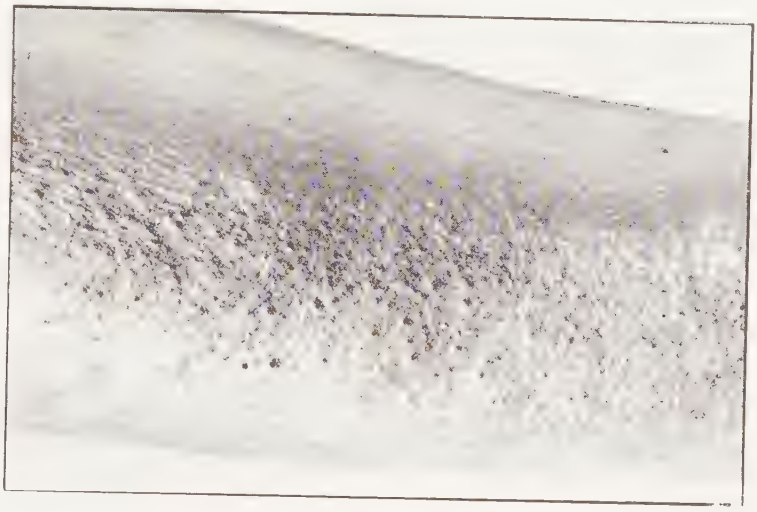


FIG. 1.—Keratosis pilaris of the arm.

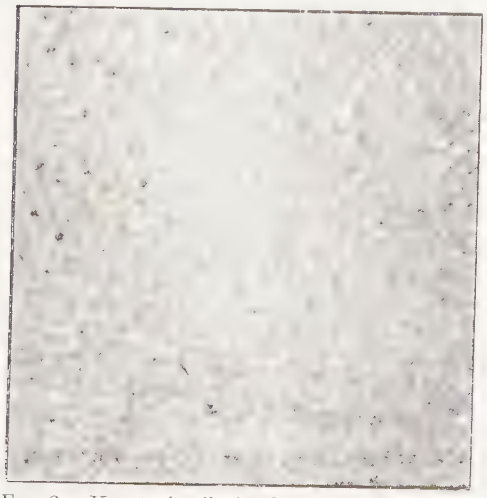


FIG. 2.—Keratosis pilaris of the abdominal skin.

The skin is generally dry and hyperkeratotic with slight ichthyotic scaling. This change is also seen over the flexures of the limbs (Figs. 1 and 2). Keratosis pilaris is present over the trunk and extensor aspects of the limbs. Her record at school is good. She was top of the class last year and won a scholarship. Her progress this year has been satisfactory except that she has become "rather slow."

Investigations.

Blood β carotene : 358 mg./100 ml.—slightly increased.
Vitamin A : 42 i.u./100 ml.—slightly reduced (Dr. W. Merrivale).
Hb : 70%.
Blood serum cholesterol : 425 mg. 100 ml.
B.M.R. : — 47% (Dr. R. R. de Mowbray).
— 37% (Dr. R. R. de Mowbray).

Comment.—I have not been able to discover that keratosis pilaris has been described as a feature of myxoedema. The follicles might be expected to show early thyroid deficiency changes, as they do with vitamin A and C deficiency. It is known that in myxoedema there is inability to change carotene to vitamin A. The diminished blood level of vitamin A in this case may be responsible for the keratosis pilaris.

The PRESIDENT : She also had a certain amount of erythrocyanosis frigida and complained a good deal of coldness of the limbs and hands. I think that keratosis pilaris is almost a constant feature of erythrocyanosis frigida. The worst case I have seen of that disorder developed big bullae in the winter, and I had to take the patient into hospital for two consecutive winters. We estimated the B.M.R. on both occasions and it was at the upper limit of normal.

Dr. C. H. WHITTLE : I think it would be very interesting if Dr. Forman could later tell us the result of treatment, and also note whether there is any change in the blood vitamin-A level after giving thyroid.

POSTSCRIPT (July 1951).—This child has been treated for seven weeks with up to 1 grain of dry thyroid a day and there has been much improvement. She has lost weight, her skin is healthier, smoother and pink ; she is more alert and responsive. The keratosis pilaris over the back has almost disappeared except for a band under the back strap of her brassiere.

β carotene is now 177 mg. and the blood serum cholesterol 220 mg. 100 ml.

Serum protein bound iodine, 3 microgrammes % before treatment, is now 9 microgrammes %.

The following cases also were shown :

Leprosy.—Dr. D. S. WILKINSON.

Leprosy under Treatment with Diamino-diphenyl Sulphone (Two Cases).—DR. E. WADDINGTON.

Leprosy.—Dr. J. LUDER (for DR. J. R. OWEN.)

BOOK REVIEWS.

THE YEAR BOOK, 1950.*

The Year Book takes on its usual excellent form and this edition will no doubt prove as valuable as those which have gone before. There are other ways of keeping abreast with modern progress in dermatology than reading this volume, but surely none more easy and more pleasant.

In the introduction the authors consider the treatment of pyodermas. First they list eight cardinal properties of therapeutic agents from which a therapeutic index is to be assessed. Against these criteria seventeen common substances are considered. From this they proceed to a detailed description of the treatment of eight types of pyoderma, which contains little, if anything, that is controversial. F. R. B.

* *The 1950 Year Book of Dermatology and Syphilology.* By MARION B. SULZBERGER and RUDOLF L. BAER. Chicago : The Year Book Publishers, 1951. Pp. 474. 66 figs. £2.

Undernutrition.*

Our knowledge of the effects of undernutrition is still surprisingly slight considering the great opportunities there are for studies in this subject in many parts of the world.

The work carried out by the medical research team in Wuppertal does much to remove this defect and the results of the investigation are full of interest. The largely negative nature of the findings may be partly due to the subjects of inquiry being in a state of severe undernutrition, but never in the last stages of starvation.

In the short space available it is impossible to do more than mention some of the positive results emerging from a large number of carefully controlled observations on the cardiovascular system, nervous system, bones, alimentary tract, urinary and hepatic function, blood and skin.

The essential changes in undernourished persons were found to be loss of fat and cellular tissue and an increase in the extracellular fluid in the body. The latter accounts for the oedema so often seen, the importance of which has been exaggerated.

Slight reduction in the birth-weight of babies was noted and in the amount of breast milk, though the quality of the milk was not altered. Children were lighter and shorter than their English and American counterparts, but were bright and healthy, though apparently rather liable to infections of the skin, possibly owing to lack of soap. Blood pressures tended to be low and the pulse-rates slow, while brisk reflexes and emotionalism were often seen. Serum cholinesterase was low.

To dermatologists the report by McCance and Barrett on the skin is of particular interest. Roughness and desquamation, especially on the legs below the knees, was the commonest observation. This was accompanied by follicular hyperkeratosis, especially of the extensor surface of the limbs. Thickening, roughening and transverse fissures were seen in many cases below the knees and in the elbow region, and ulcers on the legs were often remarked. Characteristic pallor was apparent in many and was commoner in men than in women.

Histological examination showed that the mouths of the hair follicles were filled with plugs of keratin and that the hairs were twisted and atrophied, as were the follicles themselves. The sebaceous glands were poorly developed, but the sweat glands were normal. The erector muscles were hypertrophied, probably as a physiological response to great activity. The subcutaneous fat was diminished in amount and the distance between it and the epidermis was greater than usual.

In discussing these changes the authors claim that the clinical and histological appearances are similar to those described by others as due to lack of vitamins A or C, and that they closely resemble, if they are not identical with, those produced in normal persons by cold and exposure. Deficiency of vitamin A or C did not, however, exist among these cases of undernutrition, and so could not account for the signs observed in the skin. The authors suggest that the lesions "are often an exaggerated response of the skin of certain people to cold, or possibly to the reduced blood supply that accompanies it", and conclude that an experimental approach is the only one likely to settle the matter. This is undeniably true, and it is unfortunate that laboratory animals are not suited to this purpose.

It is well to be reminded that follicular keratosis, xerodermia and pigmentation occur in more than one condition, and that the assumption that phrynoderma may be caused by vitamin A deficiency alone is not proven. Not every dermatologist, however, will accept the view that the changes described can be produced in the normal skin of certain persons by cold alone.

The excellent photographs, some of which suggest ichthyosis, add to the interest of this section of the report, which will be of the utmost value to other workers in the same field.

A. D. P.

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* *Studies of Undernutrition, Wuppertal 1946–9.* Medical Research Council Special Report Series No. 275. London: H.M. Stationery Office. Price 12*s.* 6*d.*

Framboesia.*

This publication is intended for doctors, nurses and auxiliary medical personnel, and was written in order to simplify the confusing descriptions contained in many books. There is no doubt that in this object the authors have succeeded. In eleven pages of text they have grouped the skin manifestations of yaws into sixteen classes. Some over-simplification is inevitable, and the text confines itself to concise clinical descriptions without differential diagnosis. It is, therefore, no more than an explanation of the 42 pictures which follow. All of the pictures are of admirably chosen cases, which make up a remarkable collection. Some of them, however, give the impression that the photography leaves something to be desired and fine detail is lost. F. R. B.

CURRENT LITERATURE.

TEMPORARY EXONICATION WITH ROENTGEN THERAPY. R. Campos Martin and R. Guix Melcior. (1950) *Actas dermo-sif. Madrid*, **42**, 305.

For curing fungous infections of the nail the authors have evolved a safe method of causing the nails to be shed after x-ray therapy, so eradicating the infection in the same manner as is done in tinea tonsurans. If a single application is given the margin of safety between therapeutic dose and skin tolerance is too small. This difficulty they have overcome by raising the Kv, diminishing the intensity of irradiation and fractioning the dose ; the technical reasons for this are given. The fingers are supported on a paraffin block, the area irradiated is 2 × 2 cm., the skin distance 11 cm., Kv 170, 0·5 mm. Cu and 2 mm. Al filters, current ½ mA giving an output of 7 r. An initial application of 350 r is followed by two of 400 r on alternate days, and after an interval of a week two or more 400 r on alternate days. Total dosage 1950 r. The nails do not fall for at least a month and are completely regrown in 6 months. For this process the authors have coined the term exonication. G. W. B.

LEPROSY CONFERENCE. (1951) *Annals of the New York Academy of Sciences*, **54**, 1 142.

"Whenever two or more leprologists meet, differences of opinion are likely to be evident on such subjects as classification, mode of transmission, specific chemotherapy, resistance and susceptibility," but the object of this conference held in 1950, says the Preface, was " to summarize and evaluate existing knowledge and to direct attention to those areas in urgent need of additional investigation." Badger opens with a short history of leprosy in the U.S.A. There several states still require every case, regardless of type, to be isolated, but New York State, into which a number of cases from abroad enter every year, does not require the disease to be notified. Badger says, " I do not believe that they can rest assured that leprosy will not spread in the North."

Hanks deals with the bacteriology of leprosy, the organism of which, it is sometimes forgotten, was the first to be seen and reported as the cause of an infectious disease in man. It has still not been grown *in vitro* or transmitted to animals. This failure to grow on artificial media or even in tissue culture cells of the natural host is the fundamental bacteriological problem of human and murine leprosy. Experiments with murine leprosy bacilli show that they burn endogenously stored materials very slowly and inefficiently, but they seem unable to obtain energy from any of the known artificial media.

Kluth describes the epidemiology of leprosy. The decline of the disease in Europe has been a most remarkable phenomenon ; one supposition is that the Black Death may have destroyed an even greater proportion of lepers than it did of the general population. How rapidly the infection can spread is shown by the figures for Nahru, where it first appeared in 1912 from adjacent islands and in 15 years had attacked at least 30% of the population. However, even in areas where it is most common, its prevalence rarely exceeds 5% of the general population.

* *Atlas of Framboesia.* By K. R. Hill, R. Kodijat and M. Sardadi. Geneva : World Health Organisation, 1951. Pp. 52. 42 figs. Price 5*s*.

The lepromatous form is the principal, if not the only, source of the disease, and young children are the most susceptible of those exposed to infection. It has been suggested that there is a cross-immunity between tuberculosis and leprosy which may be the cause of the decline of the latter in some areas where the former has become prevalent, but the inhibiting factors have not yet been identified.

On the pathology and pathogenesis Fite remarks that little has been added to the classical histopathology of the nodular form that was worked out half a century ago in Europe. The patient is saturated with an infectious organism that is incapable of destroying cells directly, is not injurious to the processes of cell life or reproduction, and yet is not easily destroyed by those cells. Some complicating device, e.g., amyloidosis, etc., is needed to kill the patient. The leproma nodule becomes a tissue so completely vascularized that every cell touches a capillary. The tissues of the patient with the lepromatous form are not supersensitive to the products of the bacillus. Whether or not he is maintained in a desensitized state by antigens from the ever-present bacilli, which, however, do possess strong antigenic properties, as shown by + reaction in other types of leprosy, is uncertain. " The maintenance of such a desensitized state would appear like life on the summit of a temporarily inactive volcano. A slight alteration in the status might easily provoke a profound inflammatory reaction in the tissues, precisely such as occurs in the severe and violent acute lepra reactions."

The tuberculoid type, which is not uncommon, is simply leprosy in the specifically sensitized individual ; the tissue reaction to the bacillus is chiefly a proliferative epithelioid cell one ; the tubercles, unlike those of tuberculosis, are usually well vascularized. To the histopathologist all leprosy is neuro-leprosy ; because the cutaneous nerves related to the skin lesions are involved in all types, the infection spreads back from terminal nerves along branches to larger nerves. The South American view that the typing of a given case of leprosy requires full consideration of the histology, the clinical features and the lepromin test is supported in this chapter.

" Leprosy stands unique in the field of infectious diseases in that the laboratory is able to aid the clinician in arriving at a diagnosis only in so far as the presence or absence of Hansen's bacillus can be detected by microscopic methods " (Soule). This microscopic method is of inestimable value in clinical classification, and is the only method for the unequivocal evaluation of chemotherapeutic substances at present. A meticulous bacterial examination is now more important than ever before, because the pronounced clinical improvement following the use of sulphone compounds is not paralleled by the disappearance of the bacilli from the tissues, though nasal smears become negative earlier than do those from the skin. The use of auramine as an acid-fast stain for the examination of bacilli in fluorescent light is a valuable technique, as it permits the use of the low-power lens and so an increase in the size of the field examined. The sulphone compounds are believed to be bacteriostatic rather than bactericidal. Within a few weeks after beginning treatment the organisms become less acid-fast and stain irregularly ; acid granulation is more conspicuous. The nose becomes negative in a few months, but the skin smears may continue to be positive for five years.

Kahn discusses the universal serological reaction in leprosy, which in the lepromatous form is distinctive and different from the pattern noted in certain other diseases. The intensity of precipitation is related to the degree of activity of the disease, and so may be helpful as a guide to therapy. He has not found any distinctive serological pattern in the tuberculoid and non-characteristic types. This aspect is elaborated by Pinto and Zeo

Feldman, Karlson and Grindlay on the lepromin test of Mitsuda give a brief account of the more pertinent observations of interest to the experimenter ; they consider certain basic aspects of the test as it concerns the clinical and investigative features of leprosy control, and also give an account of the tests when carried out on apparently healthy dogs.

On the detection of leprosy by the dermatologist Reiss agrees with others that proficiency depends more on practical experience than familiarity with the written description of the lesions, and from his nineteen years' experience in the Far East he says " there is hardly a skin disease which could not be masked under the veil of leprosy." This short chapter, which is well illustrated, will be more directly interesting than the others to dermatologists, unless they have a special concern with leprosy.

The introduction of the slit lamp into ophthalmology was followed by new and detailed descriptions of diagnostic and distinguishing characteristics of ocular leprosy which are described in Elliott's contribution to the symposium.

The bacillus of murine leprosy, though so far still not cultured *in vitro*, is less refractory than Hansen's bacillus for experimental infections and investigations. It is influenced by chemotherapy, and has a special place in the evaluation of new remedies. The sulphone drugs have been the most important advance ever made in the treatment of leprosy, because they have

materially altered the outlook for the patient and for the cure of the disease and their use has been associated with few serious reactions. "The most staisfactory mode of administration from the standpoint of cost and convenience is the oral route. Sulfoxone sodium and sulfetrone may be given by this method." Dihydrostreptomycin is effective for enhancing regression of specific leprous lesions and, probably by repressing secondary invaders, its action on mucous membranes is especially rapid. Severe side actions preclude long or intensive courses with this drug.

A paper on the social stigma of leprosy, a matter that retards control and cure of the disease, is followed by a final one on control, the only method of preventing the spread of infection.

This symposium must be read by all leprologists, and dermatologists in temperate climates will do well to dip into it for interest and for information. G. W. B.

CROSS SENSITIZATION. A. Tzanck, E. Sidi and S. Dobkevitch. (1951) *Acta allergol.* (Supplementum 1), 3, 148.

The authors produce clinical and experimental evidence to show cross sensitivity between paraphenylenediamine, the sulphonamides, novocaine, paraminosalicylic acid and other substances of similar composition. All are para di-substituted benzene derivatives, and this particular chemical construction seems particularly liable to produce cutaneous sensitivity.

H. T. H. W.

HYPERSENSITIVITY TO STREPTOMYCIN. Prof. Soderbolm. (1951) *Acta allergol.*, 3, 329.

Intracutaneous and patch tests with streptomycin and dihydrostreptomycin were made on twelve non-exposed and non-allergic subjects. Positive intracutaneous reactions were given to 1/10 and 1/100, but none to 1/1000 solution. No positive reactions were given to patch tests using solutions of these strengths. Skin tests of exposed patients and hospital staff showed that positive reactors were confined to a group of nurses. One case of severe hypersensitivity to streptomycin was successfully hyposensitized, but the technical details of the procedure are not given. H. T. H. W.

TREATMENT OF PEMPHIGUS VULGARIS. Z. Balikova and R. Cervakova. (1950) *Cesk. Derm.*, 25, 254.

Review of 12 cases treated during the past five years. Germanin perhaps the most reliable remedy employed. It appears also worth while to try diuretics for prolonged periods and possibly massive doses of vitamin D_2. Penicillin was valueless; newer antibiotics were not used except for streptomycin (without improvement) in one case. J. M.

INJECTION TREATMENT OF INTERNAL PILES IN PATIENTS SUFFERING FROM PRURITUS ANI AND PERIANAL ECZEMA. J. Brodan. (1950) *Cesk. Derm.*, 25, 271.

5000 patients were treated with submucous injections of quinine and urethane. Maximum single dose injected 0·5 c.c. 60–70% of the patients were cured and a further 10–20% were greatly improved. J. M.

TREATMENT WITH VITAMIN D_2. K. Konickova-Prochazkova. (1950) *Cesk. Derm.*, 25, 285.

The author reviews the therapeutic effects in 82 cases. The best results were obtained in the treatment of lupus vulgaris; other forms of tuberculosis of the skin were less amenable. Sarcoidosis responded well, also 30 cases of lichen planus. Treatment was carried out according to Charpy's routine. J. M.

TREATMENT OF PSORIASIS BY X-RAY IRRADIATION OF THE SEVENTH CERVICAL VERTEBRA. J. Maresova. (1950) *Cesk. Derm.*, 25, 297.

166 patients were treated. A single dose of 100 r was given at a focal distance of 30 cm. with 120 Kv, 6 mA and filtration of 4 mm. Al. The results after six weeks were as follows:

Cured, about 34%; improved, 38%; unchanged, 10%; worse, 2%; whilst 16% of the patients did not attend for review. J. M.

PROGNOSIS OF LUPUS VULGARIS IN RELATION TO PULMONARY TUBERCULOSIS. O. Valentova. (1950) *Cesk. Derm.*, 25, 345.

Over 1650 cases of lupus vulgaris were investigated, and it appears that tuberculosis of the lungs, however severe, does not effect the course and prognosis of lupus vulgaris. J. M.

POTASSIUM IN THE TREATMENT OF SCLERODERMA. J. Trlgar, V. Movs and O. Kupcokova. (1951) *Cesk. Derm.*, 26, 1.

The authors claim rapid improvement by repeated intra-cutaneous injections of a 1% aqueous solution of potassium chloride into the sound skin in the vicinity of the affected area. J. M.

BALANOPOSTITIS CAUSED BY CANDIDA. V. Sedlacek. (1951) *Cesk. Derm.*, 26, 64.

Four cases are described. Aetiology was confirmed by microscopical examination and culture. The clinical picture varied greatly. All patients have had previous attacks. Relapse could be provoked by local application of 5% glucose solution. Examination of the patients' wives revealed monilial vulvovaginitis in one and a positive past history was given by another. Treatment is difficult. Gentian violet 2% watery solution was found to be the best local application, but autogenous vaccine or desensitising vaccine prepared from Candida strains or even circumcision may be necessary. J. M.

ARSENICAL DERMATITIS AND KERATITIS. J. Janku and O. Hornstein. (1951) *Cesk. Derm.*, 26, 181.

Keratitis complicating a case of generalized arsenical dermatitis during anti-syphilitic treatment is described. The authors consider the keratoconjunctivitis to have been an allergic manifestation. J. M.

NITROGEN CONTENT OF THE EPIDERMIS. J. Horacek. (1951) *Cesk. Derm.*, 26, 190.

Tangential sections of the hyperkeratotic sole of the foot were examined. The uppermost layer of the epidermis is rich in nitrogen, whilst the nitrogen content of the deeper layers is less. At the level of the stratum lucidum and particularly stratum granulosum there is a characteristic rise in the N content, which falls in the stratum Malpighii to rise again at the epidermo-dermal junction. High N content in the different layers coincides with increased amount of water present. J. M.

TREATMENT OF PLANTAR WARTS WITH ELASTOPLAST AND PODOPHYLLIN. D. A. Duthie and D. I. McCallum. (1951) *Brit. med. J.*, ii, 216.

There has been an increase in the incidence of plantar warts judged by the hospital statistics. Of the various treatments, expert radiotherapy is the method of choice for the solitary lesion. For multiple or mosaic warts, elastoplast occlusion is found effective in 60% of cases, but the combination of this method and podophyllin gave a higher percentage of cures, the duration of treatment being about the same. Podophyllin is only useful as an adjuvant to elastoplast. No assessment is made of the value of CO_2 snow or formalin bathing. B. A. T.

PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) AND CORTISONE IN DISEASES OF THE SKIN. 1. PEMPHIGUS VULGARIS AND OTHER BULLOUS DERMATOSES. A. B. Cannon, J. G. Hopkins, G. C. Andrews, H. F. Colfer, P. Gross, C. T. Nelson and C. M. Howell. (1951) *J. Amer. med. Ass.*, **145**, 201.

Seven patients with pemphigus vulgaris were treated with ACTH and/or Cortisone. Most of them received an antibiotic simultaneously to control secondary infection. Two patients died, but the 5 survivors were greatly improved although the disease was still active. Although the therapeutic effect is considered to be greater than the authors have observed with any other treatment, there is little evidence that the basic causative factor is influenced.

Two "pemphigoid" eruptions obtained almost complete remission of symptoms, but continued treatment was required to prevent relapse.

Two cases of dystrophic epidermolysis bullosa were unaffected. A. J. R.

MONILIAL INFECTIONS COMPLICATING THE THERAPEUTIC USE OF ANTIBIOTICS. J. W. Woods, I. H. Manning and C. N. Patterson. (1951) *J. Amer. med. Ass.*, **145**, 207.

Twenty-five patients receiving penicillin, chloramphenicol or aureomycin developed clinical moniliasis. Twenty or them had taken the antibiotic orally for a sore throat, and the moniliasis developed within 24 to 72 hours. It is suggested that the antibiotics by suppressing the bacterial flora competing for nutrition in the same substrate allow monilial multiplication. A. J. R.

FASCIAL HERNIAS OF THE LEGS. M. E. Obermayer and J. W. Wilson. (1951) *J. Amer. med. Ass.*, **145**, 548.

At a point about 15 centimetres above the external malleoli there is a hiatus in the deep fascia, where it is perforated by a communicating vein. At this site small fascial hernias may appear

as soft non-tender nodules on the legs of athletes or mountaineers weeks or years after trauma or physical strain. A. J. R.

PLASMA L.E. TEST IN SYSTEMIC LUPUS ERYTHEMATOSUS. J. R. Haserick. (1951) *J. Amer. med. Ass.*, **146**, 16.

The plasma L.E. test is diagnostic of systemic lupus erythematosus and is particularly valuable where the clinical picture is atypical. Diagnostic problems such as rheumatoid arthritis of an unusual type associated with a false positive Wassermann reaction and epileptic convulsions may be confidently solved if a plasma L.E. test is positive. The test remains positive during remissions longer than any other laboratory test at present in use. It is evidence of systemic involvement and is not directly of prognostic value. A negative L.E. test may occur in systemic lupus erythematosus in cases where the gamma globulin is abnormally low. A. J. R.

RINGWORM OF HANDS AND FEET. J. H. Mitchell. (1951) *J. Amer. med. Ass.*, **146**, 541.

The first part is devoted to an interesting historical review of American publications on ringworm of the hands and feet, a subject on which the author has made many important contributions. There follows a refreshingly critical review of current treatment, and the author points out that surprisingly little advance has been made and that really effective preparations are still not available. He finds caprylic, propionic and undecylenic acids of little value in practice, and has succeeded in establishing that *Microsporum audouini* grows well in media to which these acids have been added. He condemns phenol-camphor as dangerous, and copper iontophoresis as time-consuming, tedious and unreliable. He has abandoned trichophytin as of little value in diagnosis or treatment. Onychomycosis remains an unsolved problem; ammoniacal silver nitrate is of no value.

There are still too many dermatologists who diagnose the superficial mycoses without microscopical confirmation. Mitchell condemns this practice strongly as many false diagnoses are inevitable. A. J. R.

ACTH AND CORTISONE IN THE ACUTE CRISIS OF SYSTEMIC LUPUS ERYTHEMATOSUS. J. R. Haserick, A. C. Corcoran and H. Dunstan. (1951) *J. Amer. med. Ass.*, **146**, 643.

Sixteen patients with systemic L.E. were treated with ACTH or Cortisone. The great value of both in the acute phase of this disease was confirmed. During crises massive doses should be given at short intervals and it is wise to administer an antibiotic simultaneoulsy. For the really acute case ACTH is preferable to Cortisone as relapses are less severe and of slower onset, but Cortisone orally or intramuscularly in large enough doses produces an even more rapid response than comparable doses of ACTH. Oral Cortisone is suitable for maintenance. A. J. R.

SKIN DISEASES IN CHILDREN. R. T. Brain. (1951) *Med. Pr.*, **225**, 173.

The common diseases of the skin which affect children are described briefly but adequately.

In view of the complexity of the condition, infantile eczema is purposely excluded from this article. H. R. V.

SKIN DISEASES IN THE AGED. J. R. Owen. (1951) *Med. Pr.*, **225**, 178.

With advancing age there is atrophy of the elastic fibres of the skin and its appendages with thinning of the epidermis and flattening of the papillae.

The blood flow in the skin also diminishes and pigmentary changes are common. An account is given of conditions of the skin which are seen predominantly after middle life.

Leukoplakia of the mouth and vulva is fully described, and for the latter, treatment with vitamin A by mouth in dosage not less than 200,000 i.u. per day is often beneficial.

H. R. V.

INDUSTRIAL DERMATITIS. J. Franklin. (1951) *Med. Pr.*, **225**, 185.

Dermatitis from contact with irritants at work may be due to direct trauma, to specific sensitivity acquired by repeated contact with the irritant or to an inherent sensitivity in the skin of the particular individual.

Diagnosis is usually easy with careful history-taking.

Treatment demands removal from the irritant, but early return to work—often to the same job—is advisable to prevent lowering of morale, with consequent development of chronic neurodermatitis. In some cases it is necessary for the patient to find some other job.

The claims made for barrier creams have not altogether been fulfilled, and for prevention of this condition more careful selection of employees is necessarily to prevent those with sensitive skins from entering occupations in which skin irritants are handled. H. R. V.

SOME RECENT ADVANCES IN THE TREATMENT OF SKIN DISEASES. E. J. Moynahan. (1951) *Med. Pr.*, 225, 187.

The therapeutic advances initiated by the discovery of the sulphonamide drugs have affected the treatment of skin diseases. A timely warning is given of the dangers of sensitization of the skin following the local application of all the antibiotic drugs except perhaps tyrothricin.

Aureomycin and terramycin have been beneficial in herpes zoster and severe erythema multiforme.

There is not yet any real effective local application for the treatment of small-spored ringworm of the scalp, but ammoniacal silver nitrate may be of use in fungus infection of the nails. Antihistamine drugs are of great use, but their side-effects are sometimes unpleasant. Dimercaprol (B.A.L.) to be effective in dermatitis caused by the heavy metals must be given as early as possible after the condition occurs. The Bisgeard treatment of varicose ulcers is mentioned, and a list is given of the conditions in which Cortisone and A.C.T.H. have had a dramatic effect.

H. R. V.

LUPUS VULGARIS. W. J. O'Donovan. (1951) *Med. Pr.*, 225, 182.

Lupus vulgaris is becoming a rare disease. A lucid account is given of its course and the author gives the following complications :

Amyloid disease, general miliary spread—this is often heralded by rapid clearing of the skin lesions.

Squamous-celled carcinoma and pseudo-elephantiasis arising from blockage of the lymphatic channels.

Although calciferol by mouth has been established as the first method of attack, the older remedies, such as Finsen-Reyn light, destruction of the nodules by liquor hydrargyri nitratis acidus or pure liquid phenol still have a place in the treatment of some cases. H. R. V.

STUDIES ON THE TREPONEMES OF BEJEL. I : HISTORY, MORPHOLOGIC CHARACTERISTICS AND STAINING PROPERTIES. E. Rizk, G. Garabedian, H. Chaglassian and A. Pipkin. (1951) *Amer. J. Syph.*, 35, 201.

" Bejel " affects a large proportion of the Bedouin Arabs in many districts in the Near East. It is highly chronic course with little effect on the general constitution. In the early stages there are mucocutaneous and periosteal lesions. Later gummata appear. The Kahn and Kolmer reactions are always positive. Treponemes are constantly found in the cutaneous and mucocutaneous lesions of the early stages. In their motility, morphology and staining characteristics these are indistinguishable from *T. pallidum.* A. M. S.

II : TRANSMISSION TO RABBITS AND OBSERVATIONS ON THE COURSE OF THE EXPERIMENTAL INFECTION. E. Rizk, E. Shwayri and G. Garabedian. (1951) *Amer. J. Syph.*, 35, 207.

The rabbit can be infected by the treponeme of bejel. The strain was propagated by six successive passages by intratesticular inoculation. The clinical course and serological reaction follow the same general pattern as in infection with other treponemes. There is not yet sufficient evidence to identify this disease with either syphilis or yaws. A. M. S.

STUDIES ON THE LIFE OF SPIROCHAETES. VII : THE LIFE CYCLE OF THE KAZAN NONPATHOGENIC TREPONEMA PALLIDUM IN CULTURE. E. D. DeLamater, M. Haanes and R. H. Wiggall. (1951) *Amer. J. Syph.*, 35, 216.

As with the Nichols type of *T. pallidum* previously reported on, the life cycle of the Kazan type, photographically recorded by means of the phase contrast microscope, proves to be complex. There are two means of reproduction : Transverse fission is the most common, especially in young cultures. In later cultures buds appear and turn into cysts, from which single spirochaetes develop. Multispirochaetal cysts also occur, having their origin both from within a single spirochaete or following aggregation of two or more. It is suggested that this may possibly indicate a sexual process. A. M. S.

CHLOROMYCETIN (CHLORAMPHENICOL) IN THE TREATMENT OF VARIOUS TYPES OF SYPHILIS. M. J. Romansky, S. Olansky, S. R. Taggart, G. S. Landman and E. D. Robin. (1951) *Amer. J. Syph.*, **35**, 234.

Within the limits of the present follow-up (5 to 6 months) chloromycetin appears to be an effective oral antisyphilitic agent. A dose of 60 mg. per kg. per day for 6 to 8 days appears to be most effective. In the case of neurosyphilis a 15-day course is advised. Reactions are infrequent, and consist of dryness of the mouth, glossitis and pharyngitis with mild diarrhoea. 1° to 2° F. of fever may occur. Vitamin B cures the tongue and pharynx. If this antibiotic is used in the treatment of gonorrhoea the same post-treatment observation for the possible development of syphilis should be carried out as in the case of penicillin, i.e., 4 to 6 months. A. M. S.

ONE-INJECTION SCHEDULE FOR THE TREATMENT OF EARLY SYPHILIS. J. Rodriquez, G. X. Schwemlein and F. Plotke. (1951) *Amer. J. Syph.*, **35**, 246.

Seventy-one patients with dark-field positive syphilis were given 2·4 million units of crystalline procaine penicillin G in peanut oil with 2% aluminium monostearate in injections of 600,000 units at 4 sites simultaneously. After a 6 to 7 months' observation period 70% were clinically and serologically negative, 21·7% showed 3 Kahn units or less, 6·6% 4 Kahn units or more, 1·7% relapsed. No serious reactions were noted. Effective blood levels were maintained by 100% for 96 hours following the one injection. A. M. S.

OBSERVATIONS AND COMMENTS ON A CASE OF ERUPTIVE HIDRADENOMA. Fr. Woringer and A. Eichler. (1951) *Ann. Derm. Syph.*, **78**, 152.

The authors show that only by serial sections can a real study of the relation of this condition with the apocrine glands be made. They conclude that despite its frequent occurrence in the axillae and pubes, apocrine glands are not concerned in the origin of eruptive hidradenoma. F. F. H.

NON-GONOCOCCAL URETHRITIS EXCLUDING URETHRITIS DUE TO VIRUS. P. Cuilleret and J. Pellerat. (1951) *Bull. Soc. Franç. Derm. et Syph.*, **2**, 125.

An extensive summary from which the authors show the varied aetiology and diagnostic difficulties of the condition. A particularly difficult problem is to evaluate the role of saprophytic organisms. As many of these infections are transmissible they should be considered in any discussion on anti-venereal prophylaxis. F. F. H.

VISCERAL MANIFESTATIONS IN THE COURSE OF THE EVOLUTION OF NON-GONOCOCCAL URETHRITIS. H. Thiers. (1951) *Bull. Soc. Franç. Derm. et Syph.*, **2**, 162.

Are these reactions metastatic infections or allergic ? The author thinks they may be both. They include joint lesions varying from a simple arthralgia to gross deformity of a joint, especially the knee, eye lesions, intestinal upsets usually preceding the urethritis by 3 to 10 days, cutaneo-mucous, cardiac (very rare), and pulmonary. An example of this latter with a fleeting infiltration of the lung was described by the author in 1950. F. F. H.

CUTANEOUS ALLERGY DUE TO PHENOLPHTHALEIN. Rabut and Serres. (1951) *Ann. Derm. Syph.*, **78**, 137.

The commonest reaction is a fixed erythema, but variants can occur which may be urticarial, oedematous, vesicular, bullous, purpuric, ulcerated or pseudo-atrophic ; occasionally there may be a diffuse scarlatiniform or purpuric rash. The exact pathogenesis is still uncertain, but it has been suggested that the fixed erythema is associated with a vasodilator reaction secondary to changes in the sympathetic system. F. F. H.

THE ROLE OF VIRUS AND "L" FORMS IN BLENORRHAGIA. P. Durel and L. J. Boret. (1951) *Bull. Soc. Franç. Derm. et Syph.*, **2**, 144.

After considerable discussion of the literature and their own observations, the authors conclude that *Chlamydozoon O.G.* certainly plays a part, but only in a minority of cases, whilst the position of "L" forms is less well defined but suggestive. The one major fact is the beneficial action of aureomycin on amicrobic urethritis and its articular and ocular manifestations. F. F. H.

SEBORRHOEIC PEMPHIGOID (SENEAR-USHER SYNDROME). M. E. Griveaud and M. J. Duverne. (1951) *Bull. Soc. Franç. Derm. et Syph.*, **2**, 90.

This is a very full summary of the evolution, histology, biology and treatment with an extensive review of the literature. The authors conclude that the Senear-Usher syndrome is a clinical reality closely related to pemphigus. Although its histology is not pathognomonic, certain features suggest the diagnosis, i.e., superficial cleavage and disappearance of the stratum granulosum. The evolution is uncertain, but the prognosis sooner or later is grave. Treatment is unsatisfactory, the most effective being also the most dangerous. F. F. H.

SEBORRHOEIC PEMPHIGOID. A. Touraine. (1951) *Bull. Soc. Franç. Derm. et Syph.*, **2**, 113.

After surveying the evidence the author concludes that this condition should be separated from the pemphigus group and established as a definite entity with the symptomatic triad of erythemato-lupoid, seborrhoeic and pemphigoid bullous lesions, and characterized by the polymorphism and variability of these elements and also by its evolution to a fatal termination. The name given above and originated by Touraine is preferable to pemphigus erythematosus.
F. F. H.

A CASE OF HAEMANGIECTASIA HYPERTROPHICANS (KLIPPEL-TRENAUNY-PARKES-WEBER). L. Ciarrocchi. (1950) *Arch. ital. di Derm.*, **23**, 197.

A full account of such a case, of which few have appeared in the Italian literature until recently. A brief account of the other published Italian cases is given and the possible varieties and aetiology are discussed. The secondary glaucoma that occasionally occurs is given some importance.
D. S. W.

ATYPICAL TUBERCULOUS ULCERS. B. Parisi and A. Longi. (1950) *Arch. ital. di Derm.*, **23**, 161.

Tuberculous ulcers are uncommon and occur usually around natural orifices; they indicate an advanced infection and are the consequence of bacillary auto-inoculation. Usually they are of a granulo-caseous or a follicular form, and animal inoculation gives, as with all types of cutaneous tuberculosis, indication of low virulence of the inoculum. Primary tuberculous ulcers also come in this group, which may be classed as typical ulcers. Darier, Jadassohn, Pautrier and others have described atypical ulcers, thought to be due to blood-borne organisms. The authors describe a case. D. S. W.

THE TREATMENT OF LUPUS ERYTHEMATOSUS WITH D.O.C.A. AND VITAMIN C. G. Scotti. (1950) *Dermatologia*, **1**, 232.

It is refreshing to find a report of unsuccessful treatment, though the number of cases was limited to eight. The author takes the opportunity to trim his subject to the prevailing fashion, and discusses at some length the theoretical application of the adaptation syndrome to the fixed form of lupus erythematosus. D. S. W.

FURTHER STUDIES ON THE MECHANISM OF ADHESIVE TAPE DERMATITIS. Samuel M. Peck, Theodore J. Michelfelder and Lawrence L. Palitz. (1951) *Arch. Derm. Syph., Chicago*, **63**, 289.

Adhesive plaster may produce three types of reaction in the skin. The first is the usual fleeting reaction which is said to be due to the mechanical removal of the plaster; the second reaction, allergic contact dermatitis, is rare; the third is common, especially if the plaster has been left in contact with the skin for five days or longer, and consists of hyperkeratosis causing blockage of sweat-gland orifices and a miliaria-like reaction, while bacteria may multiply under the plaster and add to the maceration and irritation. The hyperkeratosis is not limited to the ostia of the sweat-ducts, but may even lead to follicular hyperkeratosis. The amount of reaction varies with the type of plaster used, and even from batch to batch of the same type. J. K.

EARLY PROGNOSIS OF LUPUS ERYTHEMATOSUS DISCOIDES. Thomas Cochrane. (1951) *Arch. Derm. Syph., Chicago*, **63**, 323.

The author ascertained the erythrocyte sedimentation rate in 83 cases of discoid lupus erythematosus and in 80 cases of other dermatoses as a control group. The former showed 79·4% with an abnormally high rate, while the control group showed 78·7% within normal limits. The

prognosis in those cases with a low ESR was better than in those with a high rate, and could be more accurately estimated if the clinical appearances were taken into account as well. Of 61 patients who responded satisfactorily to treatment 5 relapsed within two years, of whom 4 belonged to a group of 8 who showed an ESR of over 10 mm. in the first hour on conclusion of treatment. 4 of the 5 showed an increase in ESR on relapsing. J. K.

NEUTROPHILS RESEMBLING L.E. CELLS IN ARTIFICIAL BLISTERS. John B. Watson, Paul A. O'Leary and Malcolm M. Hargraves. (1951) *Arch. Derm. Syph., Chicago,* 63, 328.

In direct smears from cantharides-produced blisters in patients suffering from acute and subacute disseminated lupus erythematosus the authors found peculiar neutrophil leucocytes containing blue-staining inclusion bodies. These cells were not found in blister fluid from normal persons, nor in cases of chronic discoid L.E.

These cells are found more frequently than are L.E. cells in sternal marrow preparations, and may be a more sensitive indicator of subacute disseminated L.E. J. K.

TREATMENT OF NEUROSYPHILIS WITH PENICILLIN COMBINED WITH ARTIFICIAL FEVER THERAPY. II : FURTHER OBSERVATIONS. Norman N. Epstein and James R. Allen. (1951) *Arch. Derm. Syph., Chicago,* 63, 419.

Though the results cannot be accurately compared with the effects of penicillin alone on neurosyphilis, the authors believe that clinical response is better when penicillin and artificial fever are used together. They recommend this combination in G.P.I., tabes, primary optic atrophy, and for those who do not respond to penicillin alone. J. K.

AUREOMYCIN AND ITS EFFECTS IN EARLY SYPHILIS : PROGRESS REPORT. Jack Rodriquez, Frederick Plotke, Seymour Weinstein and William W. Harris. (1951) *Arch. Derm. Syph., Chicago,* 63, 433.

The authors treated 67 patients with dark ground positive syphilis with 70 g. aureomycin orally in $11\frac{1}{2}$ days. Spirochaetes disappeared from superficial lesions in an average time of 39 hours ; the results show that this treatment is effective in early syphilis. J. K.

GRANULOMATA EOSINOPHILICA CUTIS. M. J. Woerdeman. (1951) Amsterdam, Holland : Drukkerij Holland N. V.

This 230-page thesis is largely devoted to a comprehensive review of the literature on the various conditions which have been described as eosinophilic granulomata. Our present knowledge of the function and significance of the eosinophil leucocytes is scanty. In discussing this subject the author raises the question of the relationship between the eosinophil and the mast cell, and draws attention to the increase in mast cells in tissue eosinophilia and their decrease when ACTH is administered.

A provisional practical classification of the eosinophilic granulomata is suggested. The localized eosinophilic granuloma of the face, which has received considerable attention in recent literature, is perhaps becoming more frequent, as no such cases were discovered in a careful examination of the histological collection of the Department of Dermatology in Amsterdam for the years 1930 to 1946. There is at present no evidence as to the cause of these lesions, but they appear to be distinct from the other granulomata in which eosinophilia occurs.

Under the name of reticulo-granuloma eosinophilicum cutis are grouped the cutaneous manifestations of the Letterer-Siwe and Hand-Schuller-Christian syndromes. Some cases have been reported with lesions clinically and histologically identical with those which may form part of this syndrome, but with no evidence of involvement of other systems over long periods. These lesions are histologically similar to naevoxantho-endotheliomata, with the addition of a leucocytic infiltrate which includes many eosinophils.

Another perhaps rather dubious group is named granuloma eosinophilicum pemphigoides. The reports and illustrations of these cases are of great interest and are worth studying, although their nature is obscure. They may resemble clinically and histologically either pemphigus vulgaris or pemphigus vegetans, but have a number of unusual features.

Finally, an heterogeneous group is described. These cases include various reticuloses and inflammatory conditions, with conspicuous eosinophilia as their main feature in common.

Although this thesis includes little that is original, it is of considerable value in providing at this stage a really thorough review of the scattered literature on a subject which has been attracting increasing interest in recent years. There is a bibliography of 251 items. A J. R.